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THE "ROMANTIC" ATTRIBUTES OF "LAWLESSNESS" AND "MALIGNANCY" IN CANCER.

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I propose to consider here briefly two of the generally accepted characteristics of cancer growth: (1) its so-called lawlessness and, (2) its malignant aggressive behavior.

1. We are told very generally in textbooks of pathology that cancer cells are lawless, that they grow wildly, contrary to all rules, without correlation, are without meaning, that they are wolves in sheep's clothing; in short, the gangsters of the body. At the outset it may be said that such views at once renounce all intelligibility of cancer growth. They thus violate the logical standpoint of causality of a natural phenomenon. In other words, the statement that cancerous growth, though atypical, is lawless, separates it from all other biologic phenomena and thus puts it beyond understanding. Such a conception, however, may not be tolerated under any pretence in any scientific inquiry, even under the cloak of a "heuristic" principle; for no matter how simply we may want to describe a natural event to the uninformed, it will never do to put it beyond natural laws or order. It is a necessary logical principle of all scientific inquiry that in Nature nothing occurs without a lawful causal chain, whether it fits into the normal scheme or whether it lies outside of it. The destructive lightning which may kill, the frightful eruptions of a volcano annihilating thousands of individuals at one time, are in fact just as lawful natural events as others which happen to support mankind and to please its self-preservation. Indeed, this consideration of causality must in the

last instance also apply to a scientific inquiry into cancer and cancer growth. The first requisite, therefore, is to find if possible the laws or order of its manner of growth. To dismiss this fundamental point with a brief statement that (contrary to all other natural phenomena) cancer stands (like a miracle) purely by itself and to deny it any law and order, defeats at once the very possibility of its understanding. Indeed, this happens often enough in present cancer research which has centered (with few exceptions) almost entirely around etiologic factors. It has thus shifted the cancer problem to an entirely false position, without proper regard to the main point of its nature. It is to be regretted that this distorted standpoint is becoming uppermost even in the minds of pathologic anatomists, who are apt to leap over this side of the cancer problem. If then, on purely *a priori* logical ground, we should hesitate to accept this conception of lawlessness of a natural phenomenon, we are at once confronted by the question: Are there any real demonstrable facts at our disposal which may lead us to a better understanding of cancerous growth, or must we confess that we are, at least at present, quite unable to detect in cancer anything which points to a consistent and definite plan in manner of growth? For it may confidently be expected that if such observations exist, they will open up the right path for the approach to the cancer problem and show us the way to follow in unfolding it. Such observations are available and have now reached a point where their more general appreciation is ripe and necessary.

Every pathologic anatomist who has observed early cancerous growth, especially in glandular organs as in the gastro-intestinal tract, will have been impressed by the fact that the growth and extensions of cancer cells follow primarily the normal prescribed arrangement of glandular construction. Thus cancer cells and the so-called tumor "autonomy" do not declare themselves independent from normal tissues at once. The earlier investigators into the cancer growth were well aware of this and have given good descriptions and illustrations of this step of cancerous progress. For example, Ribbert as well as Borst have repeatedly described and illustrated such pictures in detail and these observations have been confirmed by others in earliest cancer growth (Versé, Böhmig). One may see here quite commonly a simple substitution of normal glandular epithelium by cancer cells which follow this architectural arrangement, so that normal tubules and acini are gradually lined by cancer cells. At this stage basement membranes are not broken but normal cells are simply lifted off by cancer cells and atrophy; the tubular lumen remains clear and the whole architectural plan of glandular tissue is preserved. Böhmig has, in quite recent convincing studies, reëmphasized this fact and also that the penetration of cancer into the deeper parts of the mucous membrane and muscularis mucosæ occurs only after the occupation of normal

glands is completed. Cancer cell growth is, therefore, at the start integrated with normal structure. I saw this years ago (1907) in the primary cancer of the liver in which, as I pointed out, cancer cells still may enter into the construction of the lobule. I stated "these (cancer) cells still entered at that time into the construction of the lobule, and showed the arrangement in rows after their individual change in cell character had occurred and no disturbance in the lobule had taken place; ample proof that these small islands were not metastases, but primary cancerous foci." It was only after these cells began to reproduce that they broke with the former arrangement and structure. I called this the incipient stage of a "cancerous" cell regeneration. Böhmig recognizes this recently as the first phase of cancer development.

Even the subsequent substitution of normal epithelium by glandular cancer cells is not particularly specific, for it occurs by other non-cancerous types, and may be observed elsewhere. Thus Homma points out the occasional substitution of mucoid epithelium by normal squamous epithelium in erosions of the cervix. Marpurgo reports replacement of epithelium in the mucous glands in the cervical canal by non-cancerous epithelium of the vaginal cervical lining. Similar observations by others have shown that in all such instances of tumor or non-tumor cell replacements, the *intensity of growth* of one kind of epithelium supersedes and replaces that of the other. Cell substitution is therefore the expression of the intensity or of the tempo of growth. Now with the continuation of the same intensity of growth there appears, after the occupation of original normal glandular tubules is finished, a necessary change in their arrangement and space occupation; that is, a renewed formation of new, now cancerous tubules and acini. But even in this second, complete cancerous phase, Böhmig was able to demonstrate that the plan of normal glandular development as laid down by Heidenhain—that is, tubular (dichotomous) division with formation of dimeres, acini, and adventitial appended glandular buds and sympodia*—is maintained throughout. The *apparently lawless growth* may therefore be reduced to that of *intensity or increased tempo of growth,* while still proceeding within the lawful order of all other glandular formations.

Böhmig has also shown by systematic studies of series of cases that the subsequent environment into which the cancerous tissue moves has a decided influence on its subsequent manner (differentiation) and intensity of growth, a fact generally well known to most pathologic anatomists. Thus growth in submucosa and subserosa is more abundant and completely differentiated than in the muscular coat. The latter shows an inhibition in number and form

* When one of the dichotomous daughter buds is forced to one side and is thus retarded in further growth, there results a "sympodial type," normally exhibited in the development of the pancreas (Neubert and Heidenhain).

of growth associated with a diminution in differentiation and thus the formation to simpler epithelial structures. In mammary cancer, Böhmig found the quantity of growth and its differentiation better and greater in the glandular lobules of the breast and within the adjoining fat tissue but decidedly restricted and abbreviated in the collagenous fibers of the stroma. Similar observations were made by him in papillary cancers. He concludes that there is a considerable influence on the manner of growth by what Heidenhain terms "the limiting function of the formative area." This suppression of quantity of growth and differentiation may be removed once more when the tumor passes on to other favorable formative fields and the former scheme and manner of growth reassert themselves. One finds this illustrated in cancers of mucous membranes (stomach, gut) which after having penetrated and extended in the submucosa for a distance, reënter the mucosa from below and replace the normal glandular cells of tubules in a new focus, imitating renewed cancer development. Ribbert and Borst have repeatedly found such illustrations. Even here the scheme of renewed growth in an original environment follows Heidenhain's laws in the unfolding of form and tissue arrangement.

This discovery appears to be of great consequence in the fate of cancers and their general behavior. Böhmig concludes that the original or acquired structural peculiarities of the environment determine to a large extent the degree of differentiation and manner of growth in the cancerous extensions and metastases. Thus a more typical adenocarcinoma occurs only in organs or tissues which structurally permit the development of a glandular scheme. If this structural environment has been altered by processes of age or by irritative or regressive tissue changes, it becomes unsuited for the development of new glandular growths. Differentiation and manner of growth are then lowered or checked. Thus also an already established glandular cancer may in its advance into new tissues change its type and manner of growth to that of a scirrhus.

It is for these reasons quite impossible to "grade malignancy" by the type of cell occurring in a particular locality for, just as in Heidenhain's laws of normal tissue development, the realization of growth in cancers is a combination of "Anlage" and environment under which cells operate. In this regard the constant interacting local reciprocal play between advancing cancer parenchyma, stroma, vessels and nerves, assumes quite a new and important aspect. Indeed, upon presence or absence of this play depends the cancer "take" or formation of the actual cancerous tumor, the possibility of its extensions and metastases. I have emphasized this importance in a number of previous publications.

The structural development of metastases demonstrates a similar order of things except that the first phase of structural adaptation to the original is omitted. But Heidenhain's law of sequence of

glandular formation to tubular dichotomous division (dimeres) and to adventitial buds and sympodial growth, is generally followed no matter in what organ or tissue metastasis occurs, unless the structural peculiarities of the new seat prevent this complete unfolding. In all instances, primary or secondary cancer growth is, therefore, directed, not lawless. These observations are, as Böhmig points out, still further supported by the constancy in the distances of tubular division of first and second order, and in size of lumina and epithelial linings of cancerous tubules, unless the new seats of growth have been subject to previous changes which will, as stated above, reflect on the tumor development.

The conclusions of these numerous observations, which have been well collected and analyzed by Böhmig, are plain: The cancerous growth is not a lawless, uncontrolled growth. It follows the general laws of development which have been laid down by Heidenhain for normal conditions. They are also open to the modifications of its environment, principally through "limitations of formative space," just as in normal differentiation. *All these features of cancer growth may therefore be reduced to one basic fact, that is, intensity or tempo of growth.* The latter is a problem into which we need not enter here as we are concerned only with the lawful order of development which characterizes cancer cells in their growth. Years ago Billroth stated that scientifically speaking there was no such thing as a special tumor problem, but only one of typical and atypical growth, and he intimated that as soon as we know more of the plans of typical growth, the atypical would naturally fall into its place. He saw this with an almost prophetic vision, for the subsequent discovery of the normal laws of growth by Heidenhain appear now plainly applicable to cancerous growths. Thus the understanding of the normal has opened the door to the understanding of the abnormal. These considerations lead directly to the second point, that of "malignancy" or "aggression" of cancer cells.

2. We are commonly told that cancer cells are aggressive, malignant. They have even been compared to gangsters. What does this really mean in sober language? Do they possess specific properties which other proliferating, moving and accumulating body cells do not possess? May they bring about a direct cancerous attack on tissues? I have had this phase of the cancer problem under study for a number of years and come to the conclusion that such specific cancerous attributes do not exist, but that these so-called malignant properties may be reduced to purely quantitative measures. I voiced this in a previous publication (1935) in the following words: "Is there really such a thing as an "aggressive" character in "malignant" tumor cells? Based on this and on some previous observations, I think this may well be doubted. It may perhaps be reduced to matters of relative nutrition and freedom of movement. The arrested, actively growing, mobile tumor cells hold,

by virtue of their primary (blood or lymph) vascular position, the first call on the nutritive material. It does not seem to me necessary to assume "specific" food substances. The withdrawal of most of the nutritive material and the local circulatory modifications caused by the presence of these growing and multiplying cells in the circulatory tracts, permit them to expand and encroach upon the stationary, wasting parenchyma. Thus an ever-widening cancerous circle and influence are established."

I had arrived at this conclusion in the study of sarcomatous as well as carcinomatous progress within other fixed tissues, for example, liver, muscle and lymph glands, in which their invasion and future progress may be readily followed. Here it could be shown that the so-called infiltrative (malignant) capacity of the tumor cells was in reality only an intracanalicular vascular advance which finally ended in tissue spaces and became intercellular and interfibrillar. There was nowhere any evidence that these fixed tissue cells were exposed to any particular "killer" action by cancer cells. Waste of tissue cells and fibers occur purely by nutritive atrophy as results of greater quantitative measures of tumor growth. Their presence within the nutritive and tissue channels of the locality interfere, of course, with the proper circulatory movements and nutrient exchange between blood, tissue fluids and tissue cells. The intervening tumor cells have first call on this nutrient material and its supply is withdrawn by them before it may come into contact with fixed tissues. To this comes the occupational pressure by the actively proliferating formative cancer parenchyma. Böhmig has quite recently (1937) made similar observations in adenocarcinomatous metastases of the liver from which he concludes that, first, solid epithelial plugs push their way forward in the lobular venules and, secondly, they lead through the formation of glandular loops to atrophy and waste of adjoining liver columns. Nowhere appeared, even to him, any specific direct aggression on liver cells, and cancerous advance is throughout all organs intracanalicular. The result is here quite similar to what occurs in these organs in other pathologic occupations of longer standing (blood congestion, exudates, non-irritating foreign material). All of these lead to quantitative disturbances and relations in the occupied areas and waste of fixed tissues. We therefore arrive at a conclusion similar to that as regards lawfulness of tumor growth: *Malignancy is also reducible to terms of intensity or tempo of growth.*

I have dealt in these lines—it must be fully understood—only with two of the important characteristics of cancerous growth. It has not been the intention to go further into the other issues of the cancer problem. What I was anxious to show was simply that if we really wish to arrive at a better understanding of cancer growth (and we must do so before we can really go much further with it, except by shots in the dark), we must get rid of all those "romantic"

ideas into which cancer investigation has fallen and in which it will completely drown unless it is once more rescued from popularization and treated purely as a problem of growth; not *"sub specie individualitatis,"* but *"aeternitatis."* These observations indicate that such a route is possible and worthwhile. I hope also that they reëmphasize the still great necessity of structural investigation of cancer in relation to its environmental determinants. Kreyberg's illuminating observations on the structural changes leading to cancer formation after tarring mark here a substantial progress in the understanding of cancerous development.

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LOCALIZATION OF CARDIAC INFARCTS IN MAN.

I. A COMPARISON OF ANTERIOR–POSTERIOR WITH MUSCLE BUNDLE MODES OF LOCALIZATION.*†

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AMONG the most rapidly developing chapters of medicine is that of coronary disease. The first combined clinical and electrocardiographic study published by Herrick[15] in 1919 has been followed by a world wide flow of publications. White[33] lists 56 papers which are only a fraction of those available.

Antemortem localization by means of the electrocardiogram was at one time not considered possible.[10,14,17] More recently there is a countertrend and multiple diagnostic criteria have evolved for which a measure of efficiency is claimed. An impetus to the latter group was derived from the observations of Parkinson and Bedford,[20]

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whose report was based on a study of 26 patients among whom were 6 deaths with 4 autopsies. A quotation from their article indicates the source of the T_1, T_3 terminology:

"Usually a definite sequence of changes in the R–T segment and in the T waves is recorded. Shortly after the onset of symptoms a transient deviation of the R–T segment occurs. This is followed by a deep inversion of the T wave in either Lead I or III but not in both, and often by a lesser inversion in Lead II. Curves obtained after a few weeks conform to one of two main types according to the incidence of T inversion in Leads I or III" (p. 204). "As a rule the R–T deviation is best seen in Leads I and III and is then constantly in opposite directions in these two leads; thus an R–T elevation in Lead I is associated with an R–T depression in Lead III and *vice versa*. Elevation in Lead I is about as frequent as depression in Lead I, . . . R–T deviation may, however, be confined to a single lead (Figs. 16, 27) or may be most evident in Leads I and II or Leads II and III."

Barnes and Whitten,[6] using the T_1, T_3 terminology, analyzed a series of 47 case histories with autopsies, 12 selected for detailed report. That it is not always easy or even possible to classify tracings as Type T_1 or T_3 is evidenced by the following quotation: "Elevation or rounding of the contour of the R–T segments in Leads I and II will serve to identify the abnormality as Type T_1 although no inversion of T is present (p. 149). Occasionally in Lead I the identification of an abnormality of Type T_1 depends on an inverted T wave in the lead with R–T characteristics preceding it which suggest infarction [p. 149]. . . . In the light of these observations we have classified our electrocardiograms into Types T_1 and T_3 and have subdivided these types into groups listed as typical, less typical, and indeterminate (p. 150)."

Crawford, Roberts *et al.*[9] showed experimentally in cats that lesions by cautery on the anterior surface of the left ventricle gave a T_1 type of electrocardiogram, those over the posterior surface and apex gave a T_3 type. those over the whole right ventricle except the base anteriorly gave a T_3 type. They mention certain "unusual" curves and in Figure 6 *A* and *B* reproduce examples which do not fit into the classification, *i. e.*, R–T_1 and R–T_3 are not reciprocal.

Wolferth and Wood[35] mention similar trouble and list the confusing factors as: "(1) The infarct may occur in some unusual position, as in the lateral wall of the left ventricle or in the right ventricle. The localizing signs of such lesions are not definitely established as yet. (2) The patient may have had a previous cardiac infarct. (3) Ten cases have occurred in our series of 104 in which contradictory signs have occurred" (p. 77).*

* See also Smith, Goodrich and Needles[29] who, in a series of 20 cases with fresh infarcts, found 6 consistent with the actual location, 3 inconsistent and 11 negative or indeterminate.

Büchner, Weber and Haager[8] also have used the T_1–T_3 classification. According to them, a coronary T wave in Lead I (in which the R–T may be elevated, depressed, or iso-electric if T_1 is negative) signifies a lesion of the anterior wall of the left ventricle. A similar coronary T wave in Lead III signifies a posterior lesion. A very sharply negative T wave in Leads I or III indicates a long standing lesion.

Robb and her collaborators[21a,b,25] have taken cognizance of the existence of the individual muscle bundles in the heart and have demonstrated in 14 dogs and 6 monkeys that injury to any one of these exercises a characteristic effect on the electrocardiogram. If more than one is injured the electrical effects are algebraically summated.

It is the purpose of this essay to illustrate the practical agreement between the topographical (anterior-posterior) and the specific (muscle bundle) modes of localization. This is accomplished first by critical analysis of already published cases and second by descriptions of new cases collected by the authors. Apparent discrepancies might arise from two sources: first, confusion in identifying T_1 and T_3 types and, second, lack of anatomical precision for location of the involved muscles.

A prerequisite for consideration of these sources is an analysis of the statement of Parkinson and Bedford[20] that R–T displacement occurs in either Lead I or III but not in both, *i. e.*, R–T_1 and R–T_3 are reciprocal. Records of experimental infarction indicate that this relation is not invariable. Thus Smith[30] shows in his Figure 2 an electrocardiogram following ligation of the left anterior descending branch of the left coronary where the R–T is elevated in all three leads (an anterior lesion). Kountz and Hammouda,[18] ligating the same vessel in dog heart-lung preparations, most frequently obtained elevation in all leads. Crawford, Roberts *et al.*[9] in Figure 6-*A* demonstrate marked elevation in all leads (a posterior lesion). Figure 8-*A* of Barnes and Whitten,[6] Figure 85-*B* of White,[33] Figure 63 of Wilson in Levy's text,[34] Figure 1-*B* of Wolferth and Wood[35] are instances of R–T elevation in all leads in man. Depression in all leads may occur; it is shown experimentally in Smith's[29] Figure 7 and is also reported by Robb.[21c] Downward drifting of R–T in all leads in human infarction is seen in Figure 9-*A* of Barnes and Whitten;[6] and Barnes[4] reports 7 other cases lacking reciprocal deviation of R–T. These are sufficient examples to establish that the T_1, T_3 classification is too simple and does not include all the possibilities.

The lack of precision in anatomic localization is also due to overgreat simplification of descriptive terms. There are three functionally separate muscles in the walls of the right ventricle, four in the walls of the left, none of which is limited to any one aspect of either ventricle. Obviously any description of an infarct which omits

either the region on a given surface or the depth of the damaged layer, is, from the anatomist's point of view, inadequate. A brief description of the ventricular muscles* and their blood supply will provide a sound anatomic basis for a correlation between the geographic and the muscle bundle modes of localization. For simplicity's sake, the most common distribution will be stated. An article dealing with variations in distribution is available.[22]

A. *The superficial sinospiral muscle* covers most of the base of the right ventricle both anteriorly and posteriorly. It has an origin around the right *A–V* ring and passes downward and forward to form the anterior horn of the left ventricle. There its *second part* plunges deeply to encircle once the apex of the left ventricle; this intramural part contributes the anterior lower third of the septum. In its *third part* it encroaches upon the ventricular cavity as the anterior papillary muscle which is mainly attached to the aortic cusp of the mitral valve. Given that an infarct over the anterior portion of the right ventricle is rare, it follows that most injuries to this muscle are lesions either of the second part in the apical anterior portion of the left ventricle and septum or in the third part, the anterior papillary muscle. The second and third portions are supplied by the distal third (or less) of the anterior descending ramus of the left coronary artery, the first part is supplied by superficial twigs of both the right circumflex and the right lateral branches of the left anterior descending.

Experimental injury to this muscle produces a characteristic change in the electrocardiogram, namely, a moderate elevation of the *R–T* segment in all three leads (expressed as +++), with a concomitant negativity of *T* in all leads. A T_1 type is the criterion of Barnes and Whitten[6] for anterior localization. Their Case 3, Figure 8-*A*, and Figures 1, 3 and 13, of Büchner, Weber and Haager[8] are instances of *R–T* elevation in all leads with an anterior lesion, located at autopsy, presumably in this muscle. Fowler, Rathe, and Smith[11] obtained moderate elevation of *R–T* in all leads when superficial twigs of the coronary branches over the right ventricle were ligated (Fig. 5-*B*), and when smaller branches to the apical region were ligated (Figs. 1-*B* and 4-*C*). In these records *T* is negative in all leads, in the more acute phases.

Vander Veer and Morris[32] offer a scholarly review of the electrocardiographic changes in the presence of pericarditis. Diverse explanations of the *R–T* shifts are reported. Some have considered local vessel compression with ischemia (Schwab and Herrmann[28] and Feil *et al.*[10,17]), and others pericarditis (Barnes[4]), to be causative. Wolferth and Wood[35] think the elevation in all leads is a summation effect of anterior and posterior infarctions (p. 82). Vander Veer

* Drawings of these muscles appear in the Am. Heart J., **10**, 287, 1935, and in the 8th (1938) Ed. of MacLeod's Physiology, p. 268, and therefore need not be shown again here.

and Morris[32] believe that an elevation of $R-T$ in all leads, especially in Lead II, along with frequent slurring of the downstroke of R, no change in the chest Lead V, and no well defined Q, are indicative of pericarditis. All their cases with such positive electrocardiograms at autopsy showed definite subepicardial myocarditis. Because this type of record can be obtained as a result of acute infarction in normal hearts, before there is time for pericarditis to develop, it cannot be said to be pathognomonic of pericarditis (Fowler *et al.*,[11] Robb[21a]). On the other hand, pericarditis with myocarditis involving the superficial muscles will give the characteristic records in the absence of infarction (Fig. 5, Part II). The inference is that any conduction interference within a muscle band will affect the electrocardiogram; but (providing similar injury to conducting tissue exists) it will not identify the etiologic agent which produced that change. It has not yet been established that prolonged interference with blood supply due to: *a*, continued external pressure; *b*, progressive sclerosis (or syphilis) with narrowing lumina; *c*, various toxins; or, *d*, slowly developing thrombosis, cause lesions in conducting tissue which differ essentially one from the other. The end result of such interferences with blood supply may well be connective tissue replacement as is also the case following recovery from acute localized myocardial infection. If this be true, the rapidity of change seen in repeated tracings will be the only help which can be expected of the electrocardiogram for differential etiologic diagnosis.[7] Even this time factor may be misleading if any other pathologic process is fulminating, for then the rapidity of changes will approach those of thrombosis. This will be especially true of thrombosis involving smaller vessels where electrocardiographic changes are less definite and may be slow. If large coronary branches are suddenly occluded, the myocardial lesion and the electrocardiogram are generally specific (see Wilson,[34] pp. 281–282). As we have recently been misquoted twice,[2a,b] let us emphasize that when we speak of conduction "along a muscle band" we are expressing the spatial orientation of the pathway on the surface of the heart without implication concerning the structure which is conducting. Because Purkinje injection techniques have not shown extension into the most superficial layer of muscle such a possibility must be considered. Lewis distinguished between conduction velocity in muscle and in Purkinje tissue, which we have been unable to do; but for this reason we still make reservations (see Robb,[21a] p. 7, Conclusion 3; Robb *et al.*,[26] p. 5; Robb *et al.*,[24] p. 6) which is very different from the naive statement that we have "recently admitted the functional activity of the Purkinje network."

B. *The superficial bulbospiral muscle* supplements the sinospiral on the exterior of the ventricles; similarly it has a *second* intramural part, and a *third* part which is commonly known as the inferior (posterior) papillary muscle of the left ventricle. It takes origin by

a small head from the anterior margin of the right *A–V* ring and by a large head from the anterior, left, and posterior margins of the left *A–V* ring. A few fibers may cross the pulmonary conus; the left fibers cover the base of the left ventricle anteriorly, laterally and

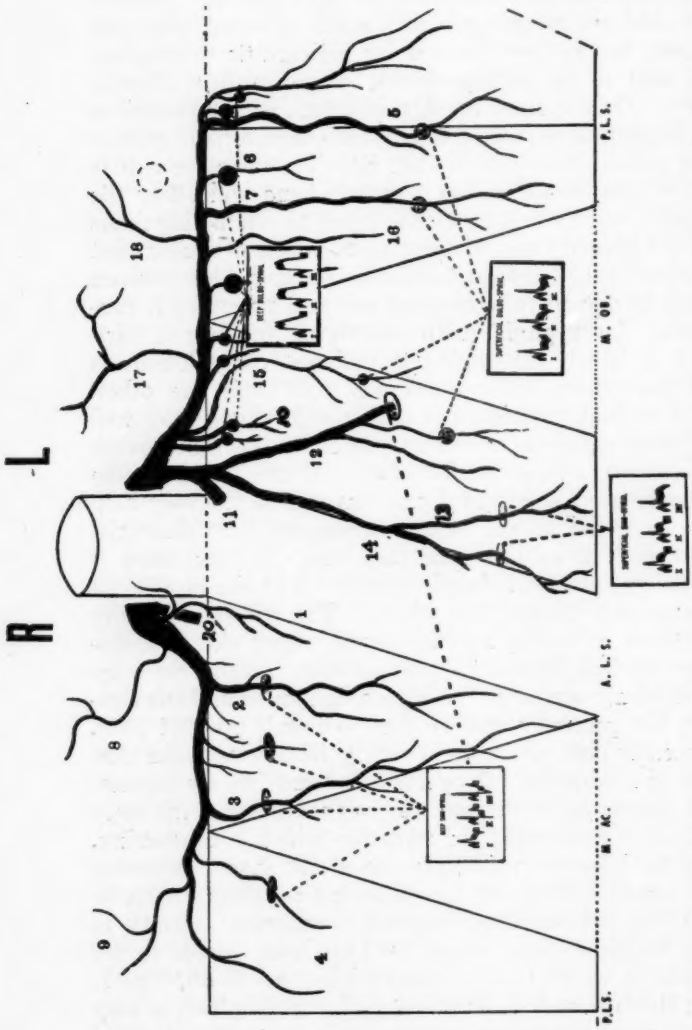

FIG. 1.—Diagram of coronary arteries (modified from Spalteholz text Figure 3) illustrating branches to individual muscles and the electrocardiograms resulting from ligation of those branches. P. L. S. = posterior longitudinal sulcus; M. Ac. = acute margin; A. L. S. = anterior longitudinal sulcus; M. Ob. = obtuse margin.

Numbered branches of right coronary artery: 1, Right adipose; 2, right anterior ventricular; 3, right acute marginal; 4, right posterior ventricular; 5, branch to posterior longitudinal sulcus; 6, posterior left ventricular; 7, accessory posterior left ventricular; 8, anterior right atrial; 9, posterior left atrial.

Branches of left coronary artery (Nos. 5, 6, 7 from left coronary in 10%): 10, left adipose; 11, septal branch of left anterior descending; 12, 13, first and second collaterals of anterior descending; 14, anterior left ventricular; 15, left obtuse marginal; 16, left posterior ventricular; 17, left anterior atrio-auricular; 18, left posterior atrial branch; 20, superior septal artery (important in animals, often reduced in man, not mentioned by Spalteholz).

posteriorly. It covers the greater part of the diaphragmatic aspect of the left ventricle and the lower (apical) diaphragmatic surface of the right ventricle, giving a few penetrating fibers to the right apex. The fibers converge to form the posterior horn of the left

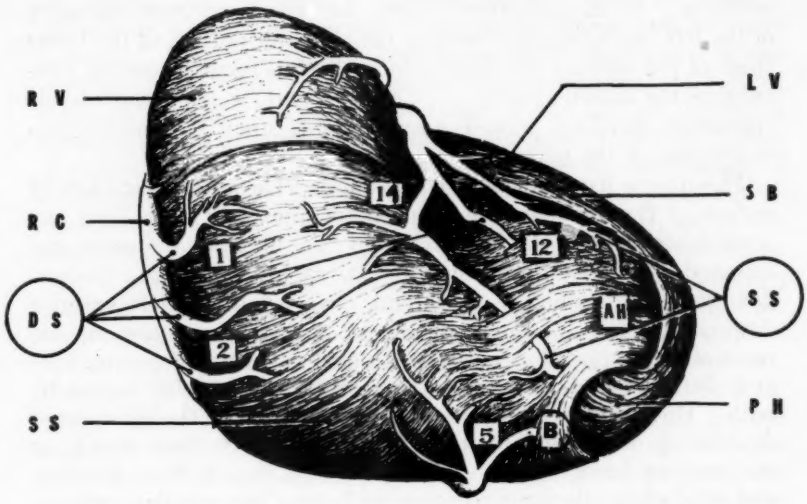

FIG. 2.—Anterior apical view of human heart (× ⅔) illustrating the blood supply to individual muscles. R. V. = right ventricle; R. C. = right coronary artery; D. S. = branches of right coronary to deep sinospiral muscle; S. S. = superficial sinospiral muscle and its blood supply; L. V. = left ventricle; S. B. = superficial bulbospiral muscle, and B = its blood supply from the posterior descending artery; P. H. = posterior and A. H. = anterior horn. Arteries numbered as in Fig. 1.

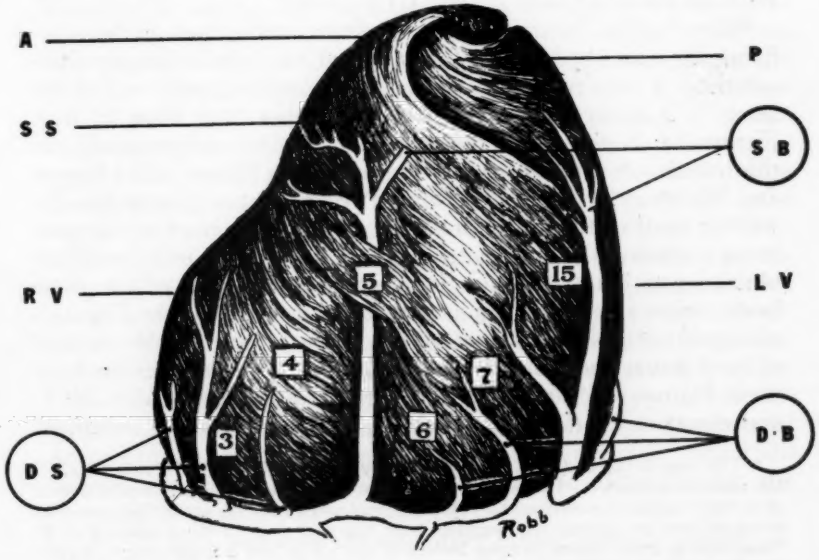

FIG. 3.—Diaphragmatic surface of up-tilted human heart. D. B. = branches from both circumflex arteries supplying the deep bulbospiral muscle. Other legends as before.

left obtuse marginal; 16, left posterior ventricular; 17, left anterior atrio-auricular; 18, left posterior atrial branch; 20, superior septal artery (important in animals, often reduced in man, not mentioned by Spalteholz).

ventricle. In its *intramural* course the muscle encircles the apex of the left ventricle once, forming the posterior portion of the lower third of the septum (to which region the superficial sinospiral contributes the anterior portion). The *third* part, which is the inferior (posterior) papillary muscle inserts mainly upon the smaller (inferior) leaf of the mitral valve.

This muscle has a multiple blood supply. The anterior and lateral regions of the first part are supplied by superficial twigs from the several branches of the left circumflex, the fibers at the conus are supplied by twigs either from the first branch of the right circumflex, or from proximal, right lateral, branches of the left anterior descending. The posterior superficial and papillary portions are more often supplied by the right coronary (about 85%), sometimes entirely by the left (5 to 10%) and often in a variable degree by both. The posterior horn also receives a supply from the left anterior descending, via lateral branches just proximal to those supplying the anterior horn; these vessels follow the muscle fiber direction and wind about the apex to enter the base of the papillary muscle. The posterior (inferior) papillary muscle is thus supplied by the left anterior descending, the left circumflex, the right circumflex, or by all three.

Experimentally a lesion in any portion of the muscle results in a characteristic electrocardiogram, R–T depression in Lead I and R–T elevation in Leads II* and III ($-++$).

Wilson[34] (Fig. 61) reproduces an electrocardiogram of this configuration with the legend "The standard leads show changes characteristic of very recent infarction of the diaphragmatic wall of the heart." Autopsy reports of Büchner, Weber, and Haager[8] with Figures 5 to 8, and 10 are further instances of lesions presumably in this muscle. Such a record is also presented in Figure 7-*C* of Barnes and Whitten[6] for which the autopsy record states: "Infarction involving most of the posterior surface of the left ventricle, the posterior portion of the interventricular septum and one of the papillary muscles was found." Their Figure 6, a photograph of the same heart, shows a posterior papillary lesion, thus verifying the diagnosis of superficial bulbo-spiral infarction. The muscle bundle method of localization would harmonize the apparent discrepancy between their Figures 5-*C* and 7-*C*, both presenting depression of R–T_1 and elevation of R–T_3, in which the former at autopsy exhibited

* The sign of the S–T deviation is generally like that in Lead III, occasionally[33] the same as in Lead I. In the electrocardiograms obtained in the presence of lesions of a single muscle in experimental animals it was noted that the entire "S" wave was involved and not merely the segment from the end of S to the beginning of T. Especially in small apical anterior lesions of the S.B.S., the S is no longer "quick" but becomes a slow deflection. In such small apical lesions of this muscle the slow, thick, shadowed S is significant even in the absence of an end-of-S-to-T depression below the iso-electric level. This observation also proved to be true in human infarction established at autopsy (see especially Fig. 8 of Part II).

an anterior and the latter a posterior lesion. Smith's[30] Figure 6 shows this same type of record 2 days after ligation of the right coronary. Otto[19] states that infarctions of the right and anterior portions of the heart (including the basal portion in that region) result in a negative *T*, and that lesion of the left and posterior portions results in a positive *T*, and so concludes that the *T* wave of the intact heart *in situ* reflects disturbances in the balance of electrical activity in the right and left halves of the heart. Here then is real confusion, for while the observations of all agree, the interpretation in one case is of the right *vs.* the left effects, in others, is anterior *vs.* posterior effects. Muscle bundle localization eliminates this conflict since this one muscle is present in all those controversial locations.

Furthermore, if more than one muscle is injured simultaneously, the electrical effect will be the algebraic summation of their individual contributions (Robb,[21b] Wolferth and Wood,[35] p. 82). Accordingly, if both the Superficial Sinospiral effect (+++) and the Superficial Bulbospiral effect (−++) are present the potentials in the Lead I would tend to neutralize each other (unless the electrical effects of one lesion greatly outbalanced the other) and the Leads II and III potentials would tend to be exaggerated. Such interpretation is compatible with the autopsy reports represented by Figures 9-*C* and 15 of Barnes and Whitten.[6]

C. *The deep bulbospiral muscle* is a strong circular muscle surrounding the mitral orifice and the aorta. In dogs, it is responsible for maintaining pressure in the aorta at the end of systole. When this muscle is injured experimentally the death rate is high, the ventricle fibrillates almost at once. Smith[29] (p. 16) produced lesions which must have involved this muscle: (branches of the left circumflex artery, which supply this muscle were ligated). He reports that 4 dogs died during the operation, 4 more died during the night and 6 survived. This mortality is 57%. In our brief series, the death rate was even higher. Legends for Smith's[30] Figure 2 and Crawford and Roberts'[9] Figure 6 make it certain that the deep bulbospiral was involved. The electrocardiograms exhibit the same excessive elevation of *R–T* in all leads reported by Robb.[21a] Similar electrocardiograms were obtained by Kountz and Hammouda.[18] During the acute stage the *T* waves are entirely positive. Three clinical instances (with 2 autopsies) of this type of electrocardiogram have come to my notice. Judging by experimental work, infarcts that would present this picture occur in those individuals who die on the street or elsewhere so abruptly that the electrocardiogram is seldom obtained.

D. *The deep sinospiral muscle* takes origin from the entire circumference of both *A–V* rings. It encircles both ventricles horizontally, surrounds the basal two-thirds of the left ventricle, lying in the plane between the superficial and deep bulbospiral. It likewise

forms much of the interventricular septum, and is the main mass of both the medial and lateral walls of the right ventricle.

There are two sources of blood supply. The right portion is supplied by all the descending branches of the right circumflex coronary artery. The left portion is supplied from some of the descending twigs of the left circumflex and particularly by the first large left collateral branch of the left anterior descending (this branch may also arise from the very beginning of the left circumflex, or from the bifurcation of the left coronary). The septal portions of this muscle are supplied by the penetrating branches of both the anterior and posterior descending arteries. It is readily seen that occlusion of the proximal portion of the left anterior descending, or the beginning of the left circumflex, or the right circumflex would involve this muscle.

The deep sinospiral has right, left, anterior, posterior, and septal portions: experimental injury to any one of these produces an electrocardiogram characterized by an elevation of R–T_1 and a depression of R–T_3 (Barnes and Mann,[5] Harris and Hussey,[13] and Gross and Calef[12]). In addition, if the septal portion is involved, there is a deep Q (this is also true for the septal portions of the S.S.S., S.B.S., and D.B.S.). Clinically, this type of lesion is common. Crawford, Roberts *et al.*[9] in Figures 1-*B* and 2, report the R–T $+--$ as an anterior lesion (apex and base). Büchner, Weber, and Haager[8] in Figures 2 and 4 present instances apparently involving the anterior portion; the septal and posterior portion seems involved in their Figure 11. Barnes and Whitten,[6] Figure 5-*A*, also report tracings of the type $+--$ in the standard leads with autopsy localization apparently in the posterior portion of this muscle. Parkinson and Bedford[20] (Figs. 4*a*, *b*, *c*, 7*a*, 8, 9) and White[33] (Fig. 84) show this configuration without autopsy support. Summation effects from coincident involvement of other muscles are also common. Probable examples of such occurrence substantiated at autopsy are given by Parkinson and Bedford[20] (Case 11, Fig. 12, "thin bulging posterior wall" indicates S.B.S. and D.S.S. involvement; Case 15, Fig. 16, "an old infarction in the septum, anterior wall of the left ventricle, and apex" probably, D.B.S., S.S.S. and S.B.S. respectively). The most frequent combination involves both the S.B.S. and the D.S.S. because they are in extensive juxtaposition with part of their blood supply from a common source. Since the R–T in the characteristic electrocardiogram for the one is $-++$ and for the other is $+--$ it is seen that if there were involvement of each, isoelectric levels might be approached in all leads. When the S.S.S., S.B.S., and D.S.S. are all damaged the R–T_1 is usually somewhat elevated and R–T_3 is somewhat depressed, also lowered voltage is often seen.

A modification of Spalteholz's[31] representation of the coronary

system is presented as Figure 1, and sketches of the blood supply to the four ventricular muscles are offered as Figures 2 and 3. It is seen that if the most apical portion of the left anterior descending is occluded, an S.S.S. lesion occurs. If an occlusion is more proximal or if it blocks twigs of Branches 12, 16, or 5, an S.B.S. lesion would result (or both). If the occlusion were still more proximal, anywhere above Branch 12 but still allowing flow in the left circumflex, a D.S.S. lesion would be present, as will also be the case when the right coronary is occluded. Finally, if the smaller descending branches of the left circumflex, the left circumflex itself, or even the whole left coronary be occluded, a deep bulbospiral lesion would be added to the picture. These anatomic facts go far in explaining the discordant results recounted by Gross and Calef.[12] Depending not only on the duration of the lesion but more particularly on the part of the left anterior descending which is occluded, R–T_1 may be slightly or very greatly elevated or depressed, R–T_3 may be elevated or depressed, and T may be positive or negative. Report of experimental procedures would be more enlightening if ligations were located not by centimeters from the origin of the left anterior descending coronary artery, but rather according to the numbered branches of these vessels (Spalteholz[31]). The distance from the origin may be deceptive, hearts vary much in size, and often the result observed and hence the interpretation depend on the ligature (or occlusion) being above or below a certain branch.

A further agreement between experimental and clinical data is found in the blood pressure measurements. Experimentally D.S.S. lesions are associated with a fall to 80 or 90 mm. Hg systolic pressure (but not the alarming falls noted with D.B.S. lesions). Parkinson and Bedford[20] reported large reductions in patients with the D.S.S. type of electrocardiogram (Figs. 4, 8, 9).

This review of the published cases of various authors illustrates the essential agreement between the topographical (anterior and posterior) and the specific (muscle-bundle) methods of localization. Among the cases surveyed, there are no glaring discrepancies, *i. e.*, no anterior or posterior localization which could not equally well be explained by muscle bundle localization. On the other hand, instances are quoted where the muscle bundle localization would reconcile published discrepancies, *e. g.*, right or left, and the "confusing cases" discussed by various authors. The muscle bundle method offers four specific types of electrocardiograms and a basis for analysis of combined lesions whereas the T_1, T_3 method of classification is shown not to include all the commonly found combinations and moreover T_1, T_3 classifications are not necessarily mutually exclusive.

References and final conclusions of Part I are appended to Part II.

LOCALIZATION OF CARDIAC INFARCTS IN MAN.

II. TWENTY-NINE NEW CASES OF MUSCLE BUNDLE LOCALIZATION WITH POSTMORTEM CONFIRMATION.*†

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A SUSPICION may arise that the autopsy descriptions previously quoted are not sufficiently exact to warrant muscle bundle localization. Data for 29 cases have been collected which demonstrate that the electrocardiographic localization given for animals is also applicable to man. Also there is evidence that where infarction occurs in an atypical position and where the T_1, T_3 classification is therefore indefinite, the muscle bundle localization is still definite and applicable.

Superficial Sino-spiral Muscle Lesions (hereafter mentioned as S.S.S.).

CASE 1.—Female, aged 63, admitted with severe pain, 48 hours' duration, 3 hypodermics given. Numbness of left arm, choking sensation. Blood pressure, 144/64. Heart sounds distant, tic-tac, irregular. Later the fibrillation ceased spontaneously. Friction rub present in 4th interspace to left of sternum. Electrocardiograms taken 2 days after the onset of pain showed elevation of R–T in all leads. Seven days later there was a second attack of pain after which the patient gradually failed (Fig. 1). Tachycardia with a pulse deficit preceded death. The moderately enlarged heart came for dissection. The right coronary was large, the orifice somewhat reduced by an atheromatous plaque. The distal portion of the left anterior descending artery was anomalous, instead of extending to the apex it ended about two-thirds of the distance to the apex, just where the branch to the anterior horn arises. This branch was completely occluded with a partly organized clot. The infarct involved the superficial sinospiral muscle including the lower third of the anterior surface of the left ventricle, the lower anterior part of the septum, and the anterior papillary muscle. A small aneurysm was present at the very apex. The fibers of this muscle at the right apex were also softened. Findings confirming the experimental work are: great pain, slight fall of blood pressure, friction rub, a lesion definitely limited to the superficial sinospiral muscle, occlusion of a vessel known to supply this muscle, and the characteristic electrocardiogram, R–T+++. This infarct was probably not the sole cause of death, contributing factors being a general arteriosclerosis, abnormal cardiac rhythm and coma of 2 days' duration preceding death (cerebral accident).

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† The greater part of the clinical material was acquired while on service at Strong Memorial Hospital, Rochester, N. Y.

CASE 2.—Female, aged 29, with chronic syphilitic endocarditis and myocarditis. Died in Strong Memorial Hospital 5 days after an acute coronary accident. Electrocardiogram showed elevated R–T in all leads (Fig. 2). T_1 diphasic, T_2 and T_3 are positive. Scarring at the left apex and a recent anterior papillary infarct with a mural thrombus were found. Again the S.S.S. muscle is found injured when the only electrocardiographic sign is a tendency for the R–T to be $+++$ in the three leads, respectively.

CASE 3.—Female, aged 69, orthopnea and edema for years. Blood pressure on admission for decompensation 210/110. Heart much enlarged. Radial and retinal vessels sclerotic. Digitalized with improvement for 1 week. Twelve days after admission to Strong Memorial Hospital the heart sounds altered and gallop rhythm was marked. There was no pain and no friction rub. During the 5 succeeding days the blood pressure fell to 130/80 and on the fifth day after onset of the gallop rhythm the patient died. An electrocardiogram taken 3 days before death, 2 after the onset of the final decline, showed elevation of R–T in all leads (Fig. 3). The T-waves in all leads were positive. Autopsy and dissection revealed no pericardial involvement. The distal portion of the left anterior descending coronary was occluded. An organizing infarct of the apical intramural myocardium (2d portion of S.S.S.) and an organizing mural thrombus were found. Cardiac dilatation and hypertrophy, generalized arteriosclerosis, chronic mitral and aortic endocarditis and an infarct of the kidney were also present. In this case, there was *no pain*, neither was there any surface lesion. The blood pressure fell over a period of days but did not reach alarmingly low levels. It is felt that this infarct itself would not necessarily have been fatal in the absence of numerous contributing factors such as prior cardiac decompensation.

CASE 4.—Male, aged 70, ambulance admission to Strong Memorial Hospital, no history. Patient comatose, aphasic and cyanotic. An E.C.G. was obtained immediately on arrival, and was interpreted by one of us as an S.S.S. type and hence probably insufficient to explain the presenting signs (record almost identical with that of Case 2). A right hemiplegia was discovered. The patient was *in extremis* and died before morning.

At *autopsy* an embolism of the left middle cerebral artery and multiple small pulmonary infarcts were found. "The heart weighs 370 gm. A mural thrombus lies at the tip of the left ventricular apex. Cut section of this area shows marked thinning of the myocardium which is grayish red and laminated. This area extends but 1 cm. from the tip of the apex, anteriorly. Right ventricle not involved. No other localized myocardial lesions, only indefinite gray scarring. Right coronary artery slightly thickened. Left descending is markedly thickened with large areas of calcification but no definite occlusion. Here is an example of chronic infarction due to sclerosis, no complete occlusion, a definite lesion limited to the S.S.S. muscle, the characteristic slight elevation of R–T in all leads of the E.C.G. is present." Death was attributed to the cerebral accident.

CASE 5.—Male, aged 70, was admitted to Strong Memorial Hospital complaining of weakness, anorexia and 30 pounds loss of weight, these symptoms having appeared during the previous 6 months. Diagnoses of "uremia with glomerular nephritis, cancer of the stomach, secondary anemia, and arteriosclerotic heart disease were made."

The heart at *autopsy* showed: Weight 400 gm. Surface red and dotted with small sandy red particles. A few delicate fibrinous bands extended across the left ventricle. Fatty plaques on tricuspid leaflets and a 4 mm. area of ulceration midway on the leaflet surrounded by stone-like material. No changes in right chordæ tendineæ or papillary muscles. Right ventricle dilated, wall 5 mm. thick. Pulmonary valves normal. Mitral leaflets thickened and present fatty plaques. Left ventricular wall 1.7 mm. thick.

Coronary openings patent. Vessels tortuous and contain some fatty plaques and some calcification. Microscopic examination: "Epithelium thickened, edematous, infiltrated with fibroblasts, mesothelial cells, wandering cells and dark staining round cells. There are masses of dark pink staining granular homogeneous fibrin on the surface. The muscle fibers are slightly enlarged, fibrous tissue and fat lies between the muscle fibers. There is perivascular infiltration." This case is reported to indicate that thrombosis with infarction is not necessary to produce the S.S.S. type of electrocardiogram (Fig. 5; see discussion in Part I).

These 5 cases illustrate the outstanding clinical as well as the electrocardiographic signs of superficial sino-spiral lesions. It is seen that the electrocardiographic picture has no etiologic significance, *i. e.*, thrombosis, sclerosis, and pericarditis with muscle involvement each produce the characteristic picture, R–T slightly elevated in all leads. These lesions were all anterior; Case 3 involved only the internal (anterior papillary) portion of the muscle; Case 5 had pericarditis with muscle involvement; Cases 1 and 2 surface and anterior papillary infarctions; Case 4 infarction of the surface portion only.

Superficial Bulbo-spiral Muscle Lesions (hereafter called S.B.S). The E.C.G. and clinical picture characteristic of S.B.S. lesions are presented in 7 cases, of which 6 were verified by autopsy.

Case 6.—Female (from the records of Dr. Jos. Sailer) was hospitalized for 3 months before death which followed repeated coronary attacks. The electrocardiogram showed marked depression of R–T_1 and marked elevation of R–T_3. A prominent Q_3 was present (Fig. 6). The heart was injected and Roentgen rayed before opening. An occlusion near the acute margin of the heart, in the right circumflex artery, was found. There was some involvement of the deep sino-spiral, but by far the greater infarction was in the superficial bulbo-spiral in its septal and posterior papillary regions.

Case 7.—Male, aged 39, whose history dates back 12 years to a picnic when the patient ate and drank heavily and then played ball. There was collapse and a 45-minute period of unconsciousness without any convulsions and without any external injury. Thereafter he was confined to bed, had electrocardiograms, and was told that he had a "blood clot in the heart." For many years afterward he had pain on effort. He was always under observation at Strong Memorial Hospital thereafter, and was known to have rheumatic heart disease and myocardial insufficiency, Class I, 5 years before death, 7 after the picnic. During the last 7 years of life he had attacks of unconsciousness which were thought to be of circulatory origin. Aortic stenosis was diagnosed. Blood pressure usually about 170/80. He fell dead after running for a street car.

At *autopsy* the heart was found to be enlarged and a high degree of aortic stenosis was present. The heart muscle was normal except at the base of the inferior (posterior) papillary muscle where the inferior (posterior) wall was about half its thickness elsewhere. The inferior papillary muscle was paper-thin, it appeared to have scarcely any muscle fibers but consisted of a thin layer of scar tissue covered by endothelium. The coronary vessels were not diseased. In this instance, there is history of but one coronary attack which may have been an embolism. Certainly the lesion was limited to the superficial bulbo-spiral muscle. The electrocardiograms taken during the last 5 years of life, that is from the 7th to the 12th year after the attack, consistently show an R–T depression in Lead I and an elevation in Lead III

(Fig. 7). It seems doubtful that "injury current" could explain these R–T displacements which lasted 12 years (Wilson[34] *et al.*).

CASE 8.—Female, aged 66, had diabetes and arteriosclerosis. Because of a gangrenous toe the left foot was amputated in Strong Memorial Hospital after which there was a cerebral accident and sudden death. Blood pressure 150/70. The electrocardiogram showed a depression of R–T_1 and elevation of R–T_3 which is characteristic of superficial bulbo-spiral lesions (Fig. 8). An old occlusion of the left anterior descending artery with a small aneurysm in the posterior apical portion of the superficial bulbo-spiral muscle was found.

CASE 9.—Male, aged 61, severe anginal attack 1 week before admission. Seven years ago had a "fainting" spell with dyspnea. Two years ago had effort pain. One year ago liver was said to be enlarged. Heart enlarged, loud harsh systolic murmur. Blood pressure 140/80. There was a dull ache in the lower abdomen for 4 days with *intense pain* one-half hour before death. Two electrocardiograms were of the superficial bulbo-spiral type (Fig. 9). The left anterior descending artery was occluded and old and recent *anterior* infarcts of this muscle found.

CASE 10.—Male, aged 51, was admitted to Strong Memorial Hospital for treatment of bronchopneumonia. He also had hypertensive arteriosclerotic heart disease. The electrocardiogram was of the superficial bulbo-spiral type, R–T_1 depressed, R–T_3 elevated (Fig. 10).

At *autopsy* an *anterior* infarction confirming the electrocardiographic diagnosis was found.

CASE 11.—Female, aged 61, progressive dyspnea for past year. Refused insurance 6 months ago (hypertension and angina). Heart enlarged, sounds poor quality, liver at umbilicus. Pulsus alternans, protodiastolic gallop at apex. Systolic pressure on admission to Strong Memorial Hospital 200 mm. Hg. The patient was restless and had sufficient pain to require opiates during a period of 19 days. Three days before death, fever appeared and the blood pressure fell to 150/95. Electrocardiograms taken on admission and again during the second week were of the superficial bulbo-spiral type (Fig. 11).

At *autopsy* general arteriosclerosis and severe coronary sclerosis were found. There was cardiac hypertrophy with dilatation. The left anterior descending artery had been occluded with old and new infarcts at the left apex posteriorly. A mural thrombus was attached to the left apex.

CASE 12.—Male, aged 45, had had 5 admissions to Strong Memorial Hospital in 2 years. Symptoms include pain, acute dyspnea, vomiting, orthopnea. The physical signs have been pallor, perspiration, edema, enlarged liver, soft apical systolic murmur, gallop rhythm. Blood pressure has ranged from 120/80 to 90/60. Four electrocardiograms taken over 2 years showed constantly the superficial bulbo-spiral characteristics (Fig. 12). Shortly after the fifth discharge the patient died at home during an attack. There was no autopsy. The case is included because of the typical history with a characteristic E.C.G. of an S.B.S. lesion, 5 known attacks preceding death.

Seven cases illustrating superficial bulbo-spiral lesions are presented, 6 of these were proven at autopsy. The clinical signs are the same as for S.S.S. lesions, *i. e.*, much pain and moderate fall of blood pressure appearing over a period of several days. Cases 8 and 11 are instances of *posterior* lesions following occlusion of the left anterior descending artery, Case 7 is a posterior papillary lesion, artery involved undetermined, Cases 9 and 10 were left anterior descending occlusions with only anterior involvement of the muscle,

Case 6 was posterior involvement from occlusions of the right coronary. Again we emphasize that the characteristic electrocardiogram appears not in association with involvement of some one artery, not always in relation to the anterior or the posterior surface but constantly in the presence of a lesion of the one muscle band.

Deep Sino-spiral Lesions.

Case 13.—Male, aged 60. (Patient of Dr. E. C. Reifenstein, Hospital of the Good Shepherd.) The chief complaint was of substernal pain, radiating down both arms, of 2½ hours' duration, associated with collapse. He had been bothered with "hyperacidity" but had no history of severe cardiac pain until the second day before admission, when it was brought on by exertion, walking after meals, and was relieved by rest. On the day of admission the pain came on early in the morning without previous exertion. It was not relieved by nitroglycerine. Two hours after the onset he was writhing with pain, covered with perspiration, face pale, the pulse full, bounding, regular, 48 to the minute. Blood pressure, 140/80. The pain gradually lessened after morphine. Twelve hours later there was still pain. The heart rate was 126, regular, and the heart sounds, which in the morning had been good, were now feeble. Moist râles were heard at the bases. The condition was thought to be very serious. The electrocardiogram taken on the first day of the severe attack shows elevation of the R–T_1 and great depression of R–T_3 (Fig. 13). All standard leads show positive T waves. The record is typical of a D.S.S. lesion. The following day the blood pressure was 90/80. For the succeeding 5 days there was slight improvement, the systolic blood pressure reached 100. Ten days after the attack the blood pressure was 108/80. The heart sounds were of better quality, no cyanosis was present and the oxygen tent was discontinued. There had been no friction rub. From the end of the second to the twelfth day pain was not a prominent feature. On the following day he complained of "heart burn." The pulse rate was 60, regular, the sounds of poor quality, the blood pressure again 90/66. There had been fever constantly from the second day on. The morning of the fourteenth day he was comfortable with no signs of congestive failure, could lie prone without dyspnea, no râles, heart not enlarged. Toward evening there were periods of irregular heart action associated with a smothered sensation, extreme apprehension, and fear of death. During these attacks he was pale, hands were blue, pupils were dilated, pulse very irregular in force, rate and rhythm. An hour later the heart suddenly failed, respiration ceased after the heart had stopped.

Autopsy (Dr. Ferguson): "The heart weighs approximately 400 gm. The left coronary artery shows marked yellowish thickening and calcification with some areas of narrowing of the lumen and other areas of apparent dilatation. Just within the orifice of the left coronary artery there is a small amount of reddish brown thrombic material which is rather loosely attached to the underlying endothelium. *Extending from the bifurcation* of the left coronary there is a mass of grayish brown thrombic material which appears to *occlude the entire lumen of the descending branch for a distance of about 3 cm.* The artery in this area shows marked calcification. The myocardium of the entire *anterior* wall of the left ventricle and of the anterior two-thirds of the interventricular septum appears markedly softened and somewhat thinned out. The endocardium of the left ventricle over the anterior portion of the interventricular septum, and the anterior wall of the left ventricle extending from just below the aortic valve to the apex, appears reddish and yellowish in color, apparently due to changes in the

underlying myocardium. Scattered over the surface, but particularly near the apex are numerous irregular masses of reddish brown thrombic material. There is a flattened mass of yellowish brown thrombic material on the endocardium of the right ventricle over the interventricular septum. On section the myocardium in the before mentioned areas shows considerable thinning with numerous irregular yellowish brown areas of necrosis and apparent hemorrhage. The borders of the areas of necrosis appear somewhat edematous. The right coronary artery shows a few scattered areas of yellowish thickening with slight calcification. The valves are without evident lesion." The 3 cm. long thrombus blocked the branch to the left portion of the deep sino-spiral muscle. Since the whole anterior descending artery was also blocked the ischemia must have involved the deep sino-spiral and the superficial sino- and bulbo-spirals. The great extent of the lesion, particularly the septal involvement makes it equally certain that the predominating terminal lesion was in the deep sino-spiral.

CASE 14.—Female, aged 73, complained of precordial stabbing pain on effort for 12 days before admission to Strong Memorial Hospital. There had been dyspnea for 2 years, edema for 1 year, and orthopnea for 2 weeks. Turning in bed or walking brought on the pain. The electrocardiogram 13 days after onset (Fig. 14) was typical of a D.S.S. lesion. Two days after admission (1 day after the E.C.G.) another acute attack occurred. The blood pressure fell rapidly from 190/100 to 60/40. The following day still another acute seizure took place and this was followed by death. No autopsy was available. The case is mentioned to illustrate pain on effort, with profound drop in blood pressure in the presence of this type of electrocardiogram.

CASE 15.—Female, aged 45, had been under care repeatedly for rheumatic endocarditis and was admitted to Syracuse Memorial Hospital with a decompensation which did not respond to treatment. She was orthopneic and much distressed by the pain of phlebitis which involved her left leg and right arm. Temperature was considerably elevated. Cardiac pain was *not prominent*. The decompensation increased and death resulted. The electrocardiogram taken 2 days before death was similar to several taken during the hospitalization (Fig. 15). Complete heart block was present. If one spaces the P waves and then considers cycles where the P does not fall on the down stroke of R the criteria of a deep sino-spiral lesion (R–T+ – –) are seen to be present.

The unopened heart was injected with bismuth-gelatine solution and Roentgen rayed. An occlusion was found in the posterior portion of the right circumflex artery. Dissection confirmed a lesion of the posterior septal portion of the deep sino-spiral, the adjoining posterior wall, and to a much less extent the posterior papillary muscle (this has a multiple blood supply). There was a chronic mitral endocarditis (stenosis and regurgitation) with a large anterior papillary pushing up to make a small funnel-shaped opening. Both the aortic and tricuspid valves were the seat of active endocarditis with many friable vegetations. The infarcted area was non-hemorrhagic, pale and mushy. The occlusion may have been embolic. There was no coronary sclerosis.

CASE 16.—Male, aged 58, was admitted for treatment of decompensation. Six weeks after digitalization, while still in the Strong Memorial hospital, he developed an arrhythmic tachycardia and suddenly died. Electrocardiograms taken on the day of admission and again 2 weeks before death showed a progressive deep sino-spiral lesion (Fig. 16).

At *autopsy* the heart weighed 790 gm. On cutting the left apex a large anterior infarcted area measuring 10 by 8 cm. was noted. The overlying epicardium was covered by a heavy white scar. The myocardium in this area was completely replaced by scar tissue. There was an overlying mural

thrombus 4 cm. thick. The coronaries were tortuous and calcified. The distal third of the left anterior descending was occluded. In this heart the branch to the left portion of the deep sino-spiral came off the left anterior descending, unusually low (distal). The size of the infarct ensures involvement of the deep sino-spiral muscle.

CASE 17.—Male, aged 44, died in Strong Memorial Hospital of papillary squamous cell carcinoma of the left kidney, with metastases. The electrocardiogram showed low voltage in all leads with *R–T* elevation in I, *R–T* depression in III (Fig. 17): Metastatic nodules were found in the anterior surface of the right ventricle, penetrating into the deep sino-spiral layer. The S.S.S. is also involved but the deep sino-spiral picture predominates.

CASE 18.—Male, aged 72, history of *effort pain.* Admitted to Strong Memorial Hospital 4 days after a coronary attack, in shock. Blood pressure, 90/50. There were tarry stools. There was no recovery from the shock; death occurred 8 days after the onset. The E.C.G. 6 days after the onset of coronary pain showed the typical D.S.S. picture (Fig. 18). The *QRS* in no lead exceeded 0.10 second. Heart block was present, *P* is on the upstroke of R_1 and quite separate from the *R* cycles shown in II and III.

At *autopsy:* General arteriosclerosis with marked coronary sclerosis. Mitral endocarditis with stenosis was present. There was occlusion in the proximal portion of the left anterior descending, above the branch to the deep sino-spiral. There was also a duodenal ulcer.

CASE 19.—Male, aged 16, had been a "blue baby." The cyanosis persisted, always cold and dyspneic on exertion. The dyspnea and cyanosis increased during his sixteenth year. Fingers and toes were clubbed. Retinal fundi dark red. Heart enlarged in all diameters. A harsh, low pitched, blowing, systolic, pulmonary murmur was heard. R. B. C. 8,100,000; W. B. C. 6200. The electrocardiogram showed a "right axis deviation," but since Leads I and III do not equal II, the degree is uncalculable (Robb and Robb, 1931[23]). The *R–T* in Lead I is much elevated, while that in Lead III is frankly depressed (Fig. 19). Such changes indicate a lesion in the deep sino-spiral muscle.

At *autopsy* a patent foramen ovale and a pulmonary stenosis were found. There was no coronary disease, the right ventricle was hypertrophied and dilated.

As previously explained, the right ventricle is mainly composed of the deep sino-spiral muscle. Also the increased mechanical load in pulmonary stenosis comes on the right ventricle. Comparable examples of D.S.S. electrocardiograms in the presence of congenital lesions involving the right ventricle are to be found in reports by Abbott,[1a] "Pulmonary stenosis with ventricular septal defect" (Fig. 68, p. 290); also Congenital Pulmonary Stenosis, the case of Alexander, Knight and White[3] (Fig. 77, p. 304). Abbott[1b] in her atlas provides an additional instance in Plate XXIII (Fig. 3 c) "complete (crossed) transposition, aorta and pulmonary artery from reversed ventricles. Ventricular septum entire, and ductus arteriosus closed. Foramen ovale patent. Dilatation of aorta and *great hypertrophy of Right Ventricle.*" This case confirms not only the electrocardiographic localization, but also supports the opinion that "coronary" waves are not specific for any one type of disease. Ten years ago one of us showed reversible coronary waves following pH changes of the perfusate in the turtle heart.[27]

Deep sino-spiral lesions are demonstrated in 7 cases, 6 of which

were proven at autopsy. The localization of the muscle involvement was as follows: Nos. 13, 16, 18 were infarcts resulting from occlusion of the left anterior descending coronary and were anterior lesions; No. 17 was a right anterior involvement, No. 21 involvement of the whole right ventricular portion of the D.S.S.; No. 15 was a posterior lesion resulting from occlusion of the right coronary. Again left and right anterior, posterior, and septal lesions are described, all having two findings in common: that the D.S.S. muscle is damaged and that the electrocardiograms show elevation of R–T_1 (or S–T_1) and depression of S–T_3.

Deep Bulbo-spiral Lesions, as already mentioned, are difficult to obtain clinically. The records of the electrocardiographic service of Strong Memorial Hospital were placed at our disposal through the great kindness of Dr. Wm. McCann. Among approximately 1000 records of deceased patients only 3 of this type were to be found. Two of the 3 came to autopsy. We do not think that any one of these 3 electrocardiograms is typical of a *pure* deep bulbospiral lesion. Experimentally, small branches can be ligated which supply this muscle alone. Clinically, involvement of this muscle would result most frequently from occlusion of the left circumflex, the very origin of the left anterior descending, or the main trunk of the left coronary artery. If these larger vessels are occluded other muscles will suffer as well. At the best, then, one can only hope to find electrocardiograms approaching the type of those characteristic of the experimental lesion together with a history and physical findings similar to the experimental picture (Figs. 1–2–3, Part I).

Case 20.—Male, aged 45, chief complaint of attacks of unconsciousness. Studies made after his admission to Strong Memorial Hospital led to a diagnosis of brain tumor for which he was operated on December 14, 1936. The tumor was found to be of vascular origin with an arteriovenous communication and was inoperable. Following the operation, he did not do well. On December 16, 1936, at 8 A.M. he had an attack diagnosed as coronary thrombosis (Fig. 20). The blood pressure dropped at once from a systolic of 190 to 110/60. The pulse became totally irregular, the blood pressure fell continuously, death occurred at 1.10 P.M. In the notes there was no specific mention of pain.

At *autopsy* the coronary arteries were found to be tortuous and thickened. The most proximal portion of the left anterior descending was found to be narrowed and was also occluded with a friable clot 8 mm. in length. There was marked thinning at the apex. "At the right lateral margin of the left ventricular wall about *one-third of the distance from the base of the heart* there is a fairly definite line of demarcation in the color of the myocardium. On the left lateral wall this color change begins about *one-third of the distance up from the apex and extends* from this point upward and laterally to join the right margin as described above. Below this area the myocardium is dull mottled and grayish yellow, above it is very deep red and meaty." Microscopic examination showed fragmentation in hypertrophied fibers, no nuclei in the area of deep redness, many neutrophils, fibrin on the epicardial surface. At the right ventricular apex section showed necrotic muscle and neutrophils. The localization to the basal third of the heart

together with a definite occlusion at the very origin of the vessel ensures a deep bulbo-spiral involvement.

CASE 21.—Female, aged 76, was admitted to Strong Memorial Hospital on July 14, 1936, complaining of headache, vertigo, nausea, vomiting and some abdominal pain. She had always been unusually strong and well. Her present illness began during a period of great heat and she gave the impression that she had heat prostration. There were râles at both bases; blood pressure was 120/90, W. B. C. 17,300; temperature 39°, heart rate 150. The lips were cyanosed and there was slight edema of the ankles. The peripheral vessels were sclerosed, the heart was enlarged and fibrillating. During 2 days she received 1.4 gm. of digitalis. On July 16, 1936, she complained of *substernal pressure*, the blood pressure fell to 98/70, the lungs were "wet" with dullness at the right base. Straw colored fluid (175 cc.) was removed. On July 18, 1936, an electrocardiogram showed an "auricular rate of 280, ventricular rate 130, left axis deviation, and myocardial damage." Some portions of a long record showed flutter and other portions fibrillation. The patient died suddenly on this day. Figure 21 was taken shortly before death. The recorded diagnosis was: "Arteriosclerotic heart disease with decompensation, heat stroke, questionable coronary occlusion."

Autopsy: "The heart weighed 480 gm. The epicardium at the tip of the right ventricle and over the left ventricle was red and granular. The left anterior descending artery was markedly calcified and *contained a thrombus at its origin.* There was considerable atheroma and calcification throughout the coronary system. The right ventricular apex was dull yellow and above this was stippling of fatty degeneration. The left ventricular apex was filled with adherent clot, 4 cm. in diameter. The left ventricular wall toward the septal side showed dull yellowish completely dead muscle. *Half the septum* was necrotic. Toward the base the muscle was firmer and reddish brown. The necrotic portion was ballooned out, the wall 0.5 cm. thick. The papillary muscles were large; one showed areas of necrosis. Microscopic examination showed fibrin on the surface with dilated capillaries beneath, edema and fibrin in the subepicardial fat, intimal sclerosis of the arteries. In the muscle extensive necrosis with vacuolated, poorly staining fibers. Again the fact that the origin of the left anterior descending artery was occluded, the extent of the infarct, especially the great septal involvement, makes damage to both superficial muscles, the deep sino-spiral and the deep bulbo-spiral certain. In the electrocardiogram the deep bulbo-spiral characteristics predominated. (Note also the presence of Q_3.)

CASE 22.—Female, aged 54, for 25 years had been known to have rheumatic heart disease, mitral stenosis and aortic insufficiency with many periods of decompensation. She was admitted to Strong Memorial Hospital on August 5, 1935, complaining of a persistent severe pain beneath the left scapula which had appeared that morning. Blood pressure, 140/80. She appeared acutely ill, was orthopneic, had no cough, was cyanosed. There were râles over the lungs. The heart was markedly enlarged with a heaving precordial pulsation, the point of maximum impulse in the 6th I. S. anterior axillary line. Action was irregular, sounds of poor quality. A loud blowing systolic and a softer diastolic murmur were heard at the apex, and a short rough systolic at the pulmonary area. Impression of the admitting officer was "chronic rheumatic endocarditis with failure, auricular fibrillation, pulmonary embolism." On August 10, 1935, an electrocardiogram showed "left axis deviation, auricular fibrillation and myocardial damage." On August 20, 1935, abdominal paracentesis yielded 2700 cc. of clear fluid. On August 25, 1935, she complained of a "pain between the shoulders," was nauseated and vomited. The heart rate dropped to 27.

She gradually improved, the heart rate rose rapidly from 50 to 120, râles appeared all over both lungs, cyanosis was marked, dyspnea extreme, blood pressure fell rapidly and death promptly ensued (Fig. 22).

These 3 histories illustrate deep bulbo-spiral involvement. One man of 45 died without pain 5 hours after his first coronary attack, 1 woman died on the same day as her first complaint of substernal pressure, and the third, a woman, died of an acute seizure during decompensation of rheumatic endocarditis and subsequent to pulmonary and axillary embolism. In each of these instances the electrocardiogram has a form characteristic of a deep bulbo-spiral lesion. All three show lowered voltage, and relatively very high takeoff of R–T in all leads, with most of the T waves positive. For a more complete review of lack of, or variations in, type of pain reference should be made to Kennedy's recent study in 200 autopsied cases.[16]

Mixed Lesions. Whether this method is of value either for empirical localization or as an aid to prognosis when disease is widespread must be considered. Seven cases (23 to 29 incl.) with histories, electrocardiograms and autopsies were obtained which did not show characteristics for any one muscle lesion. At autopsy, all 7 proved to have 2, 3, or 4 muscles involved. To conserve space the protocols of 2 only (Cases 23, 26) are offered. The electrocardiograms of Cases 27 and 28 are reproduced so that the compound forms may be recognized.

Case 23.—Male, aged 68 (patient of Dr. W. E. Barnett), had been hypertensive for 20 years and had had a coronary attack 10 years ago. On June 13, 1937, there was increased anginal pain. The blood pressure was 220/160. The electrocardiogram (Fig. 23 *A*) shows the down stroke of R_1 thickened, S–T_1 slightly depressed, S–T_3 but slightly elevated. Such a combination indicates more than one lesion. Another attack of thrombosis occurred on June 16, 1937, after which the blood pressure fell to 110/70. Record 23 *B* taken 2 days later shows a further depression of S–T_1 and elevation of S–T_3. Death came on June 21, 1937. The uncut heart was sent for examination; it was large, unusually blunt and also discolored at the apex. The right ventricle was unduly small, the right auricular appendage undeveloped, the left appendage infarcted. The coronary vessels were unusually large, tortuous, calcareous, and the left anterior descending occluded below the branch to the deep sino-spiral. The blunt apical region, about one-third of the whole heart, was covered by a subendocardial hemorrhage 1 cm. thick. A large aneurysm occupied the whole apical region. On section, it was difficult to distinguish the muscular wall, both superficial muscles were replaced by scar tissue. The hemorrhage was contained in the sheath of these muscles.

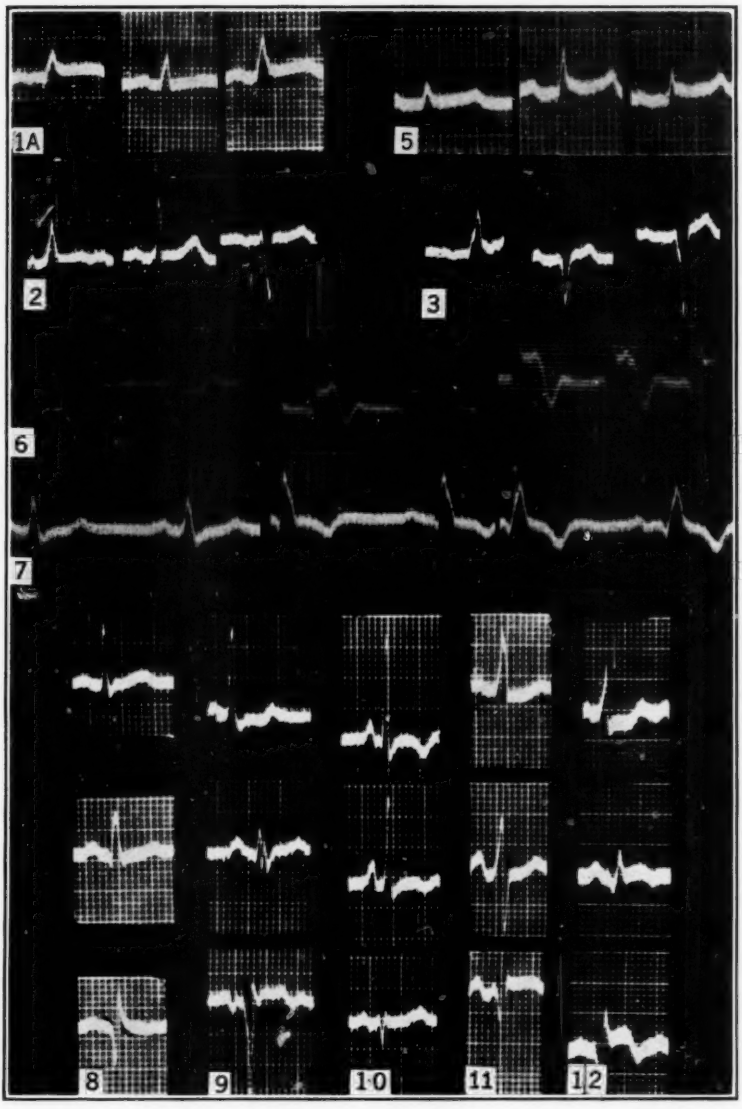
This extensive involvement of both superficial muscles in an individual having a blood pressure of 220/160 supports the experimental observation that these muscles are not responsible for the maintenance of the circulation. Anterior and posterior walls were about equally involved which may have made T_1–T_3 localization less satisfactory.

CASE 26.—Male, aged 63 (history reported through courtesy of Dr. W. D. Paul from the service of Dr. Fred Smith, University Hospitals, Iowa City), had had thyroid treatment for myxedema for 5 years and had repeatedly stopped the medication because of substernal pain. Shoveling coal induced an attack followed by 4 hours of unconsciousness, after which he was admitted to the hospital (December, 1934). Upon admission the blood pressure was 125/70 though it had previously been up to 170/100. There was marked retinal sclerosis. He improved and remained in the hospital as an ambulatory patient, again taking 5 grains of thyroid extract (B. W.). On January 15, 1935, at 7 A.M., a severe attack of pain necessitating morphine occurred, and after 5 hours another excruciating attack was experienced. Electrocardiograms were taken at 8 A.M. and at about 2.30 P.M. and again a few minutes before death ½-hour later (Fig. 26). Records taken in 1929 show S–T_1 depression and S–T_3 elevation, an S.B.S. lesion which could have been caused by the narrowing of the distal portion of the left anterior descending artery. This type of record persisted but in the tracing taken an hour before death the voltage has decreased a little and the S–T_1 depression is less as is also the S–T_3 elevation. The clinical history of another severe attack of pain plus this change is interpreted as indicating involvement of the more basal muscles. The D.S.S. (+ − −) added to the S.S.S. and S.B.S. would explain the change. Finally, a few minutes before death, the R–T takeoff begins at the very peak of R which is characteristic of D.B.S. lesions. The heart weighed 520 gm. There was an area 1 cm. in diameter on the anterior surface with a recent fibrous adhesion. At the apex and posteriorly were numerous depressed gray areas. On cut section, the apex, the greater part of the posterior wall, part of the septum and part of the anterior wall all show scarring. In some places the muscle is almost replaced by scar tissue. The lumen of the coronary vessels is reduced, there is a fresh occlusion of the right posterior descending and the left anterior descending is so sclerosed as to be almost obliterated. The last finding accounts for the persistent S.S.S. and S.B.S. involvement and the recent occlusion for the involvement of the D.S.S. and terminally of the D.B.S. Using the muscle bundle method of analysis the progress of coronary disease can be visualized and related to the progressive anatomic changes. Anterior *vs.* posterior localization could scarcely have been so satisfactory since both anterior and posterior lesions were present.

Analysis of such cases justifies the inference that in the presence of signs and symptoms of coronary disease, if the electrocardiogram does not conform to one of the four types described for localization, more than one muscle bundle has been injured.* When a progressive change from one characteristic type to another is found, especially with lowered voltage appearing, the prognosis is more serious because more muscles are being damaged.

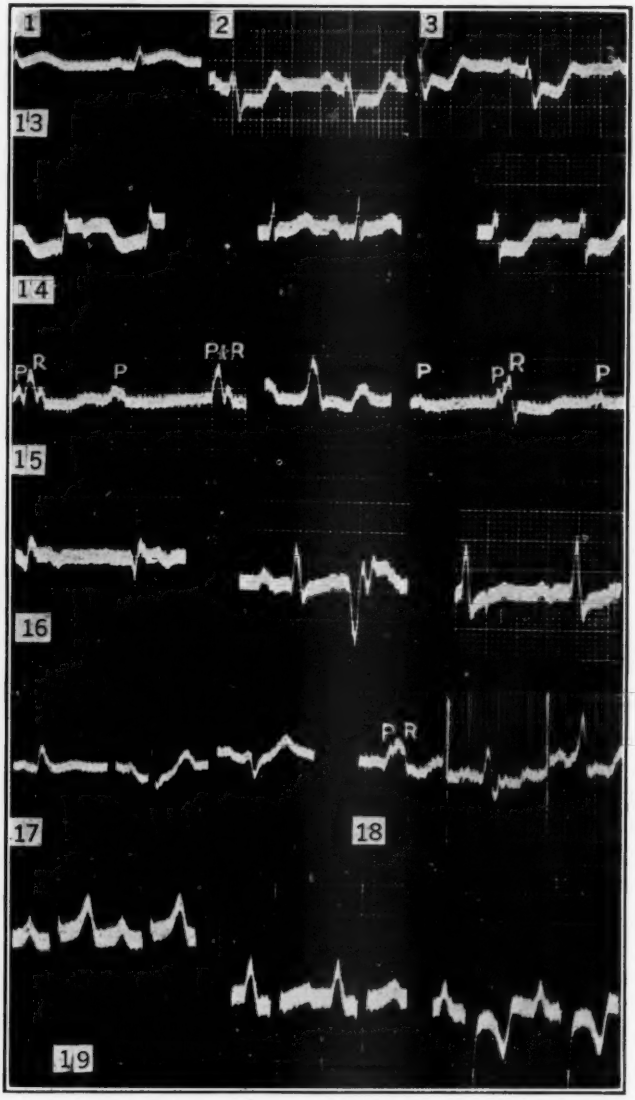
Summary and Conclusions (Parts I and II). 1. The T_1, T_3 method of localization is valuable where infarcts occur in the more common localities and under these conditions there is close agreement with the muscle bundle method.

* None of the electrocardiograms reproduced by Wood, Wolferth and Bellet[36] as examples of left lateral localization are typical of single muscle lesions and would have been interpreted by us as "mixed" lesions. (No infarcts of this region with the possible exception of Case 23 were present in our whole series, which reflects its relative rarity.) Our Figure 1 (Part I) shows that the left circumflex artery supplies four muscles in the left lateral region of the ventricle, hence its occlusion would inevitably produce a mixed lesion. Furthermore, Vessel No. 17 of the left circumflex is distributed (together with No. 8) to the S. A. node. This fact is the anatomical basis for their conclusion that left lateral infarction and auricular fibrillation are often associated.

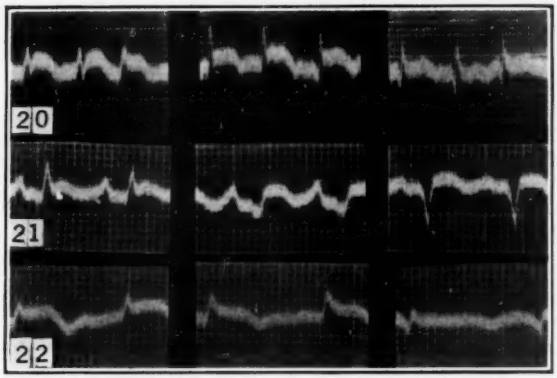


FIGS. 1, 2, 3, 5.—Electrocardiograms for cases of similar numbers. Note moderate elevation of R–T in all leads. In each instance the lesion was limited to the S.S.S. muscle, E.C.G. for Case 4 omitted, since essentially like Case 2. Three standard leads arranged horizontally.

FIGS. 6 to 12.—For cases with same numbers. Each shows R–T_1 depressed and R–T_3 elevated, in each a lesion in the S.B.S. muscle was found. Three standard leads were arranged horizontally for Cases 6 and 7, vertically for all others. Figs. 8 and 11 were associated with posterior lesions from occlusion of the left anterior descending artery; Fig. 6, was present with a posterior lesion following occlusion of the right circumflex artery; Figs. 9 and 10 are from anterior lesions with occlusion of the branch of the left anterior descending to the S.B.S.; Fig. 7, taken 12 years after an embolism which involved the inferior papillary portion of the S.B.S. only. There was no coronary disease but a marked aortic stenosis. Five similar E.C.G.'s taken respectively in 1930, 1931, 1933, May, 1935, and October, 1935, following the single coronary attack in 1923 are on file. The R–T displacements are present after 12 years.



FIGS. 13 to 19.—All show elevation of R–T_1 and depression of R–T_2. Each proved to have a lesion in the D.S.S. muscle. In Cases 13, 16, 18 the occlusion was in the proximal portion of the left anterior descending and the lesion was anterior. In Case 15 the right circumflex was occluded near the posterior sulcus, the blood supply to the bundle of His was interrupted, block resulted. There was a large posterior infarct. Case 19 shows the same R–T displacements where the muscle injury was due to overwork and overdistention in the presence of congenital pulmonary stenosis. There was no coronary disease. Case 17 had a cancer nodule in the right anterior portion of this muscle.



FIGS. 20 to 22.—The characteristic to be noted in these D.B.S. lesions is the relatively very high takeoff of the R–T in all leads. There is commonly lowered voltage and a tendency for the T waves to be positive in these badly damaged hearts.

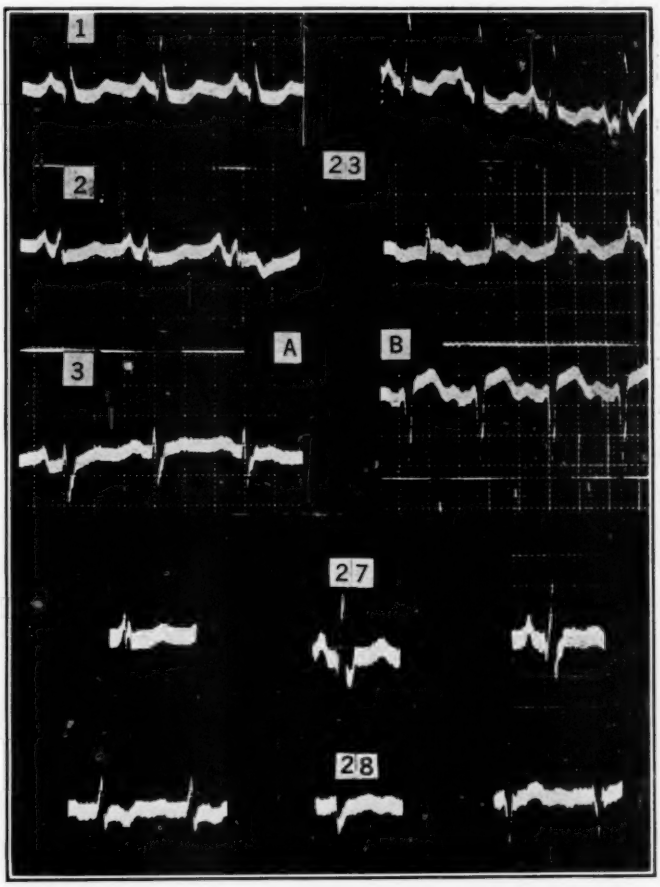


FIG. 23.—E.C.G. taken 10 years after one coronary attack and 2 days after another. Fig. 23 *b* taken 2 days after *a*. An S.B.S. lesion is surely present and probably an S.S.S. too because the S–T_1 is more nearly iso-electric than one would expect with the degree of R–T_3 elevation present. Both were found to be replaced by scar tissue at the apex where an aneurysm large enough to hold a golf ball was found. Anterior and posterior walls were about equally damaged. Electrocardiograms of Cases 24, 25, 29 are not reproduced since they are fairly similar to those of Cases 27 and 28.

FIGS. 27, 28.—It is seen that these records do not conform to any one of the four characteristic types. Multiple muscle lesions were found in each.

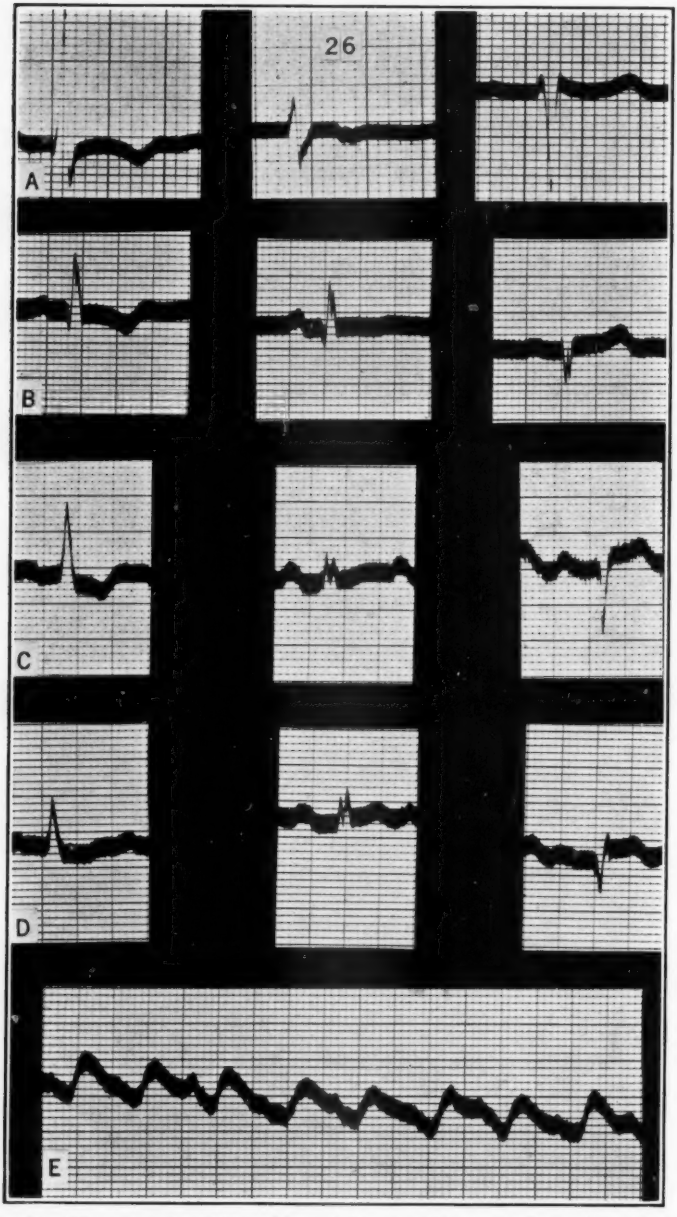


FIG. 26.—Five records of Case 26, *A* taken in 1929, *B* in December, 1934, *C*, January 15, 1937, at 8 A.M., *D* the same day at 2.30 P.M., and *E* a few minutes before death at 3.00 P.M. Note the progressive change in the *R* contours and in voltage. An older S.S.S. and S.B.S. lesion is complicated by a D.S.S. and just before death by a D.B.S.

2. Numerous authors report difficulty in localization when the infarcts involve an unusual site. When a reciprocal relation of T_1 to T_3 is lacking, application of this principle becomes difficult. It is shown that this reciprocal relation often is lacking.

3. The muscle bundle method of localization, supported by experimental work, has been applied to the analysis of 77 cases, 48 with adequate autopsy reports from literature and 29 new reports. When one of the four characteristic electrocardiograms appears there is no doubt as to the muscle involved but to specify which portion, or the extent of the lesion, or the cause of the disturbance in conduction within the one muscle bundle is not possible.

4. A short review of the superficial and deep bulbo- and sinospiral muscles together with their function and blood supply is offered.

5. As a "thumb nail" diagnostic method one may ignore Lead II and note that R–T_1 depression indicates involvement of the S.B.S. muscle; if R–T_3 is depressed the D.S.S. must be implicated; an S.S.S. lesion raises both R–T 1 and 3 above the iso-electric level. R–T takeoff from the peak of R (or near the peak) in all leads, especially in the presence of low voltage, indicates a D.B.S. lesion. Inequality of the R bases is to be sought and its presence is more instructive than its amplitude.

6. Clinical findings may fortify the experimental conclusions and the E.C.G. interpretation in the following respects: Severe pain is often present when the superficial muscles are involved and if the lesion is anterior a friction rub may be heard. Deep muscle injuries precipitate large and abrupt falls of blood pressure associated with variegated and atypical pain sensations generally accentuated by effort.

7. Inference as to etiology from the E.C.G. alone is not justified since many different pathologic changes may result in a similar effect on conduction.

8. Displacements of R–T do not disappear as rapidly clinically as when infarction is experimentally produced by ligating a vessel in an otherwise normal heart, for seldom does one find in man occlusion of one vessel without disturbance of the collateral circulation (See Gross and Calef[12]).

9. We confirm the findings of Harris and Hussey[13] and of Gross and Calef[12] modifying the conclusion of the latter to read "occlusion of the left anterior descending coronary artery *proximal to the branch to the D.S.S. and distal to the origin of the circumflex branch* results in R–T_1 elevation and R–T_3 depression." It is shown that this type of record can be obtained from right and from posterior lesions as well.

10. The superficial muscles may be infarcted repeatedly and death may ensue when a deep muscle is eventually involved, or from some non-cardiac cause.

11. The prognosis for D.S.S. lesions is graver and treatment of an attack should be more rigid and much more prolonged.

12. Infarcts of the D.B.S. are even more serious and often result in sudden death.

These data could not have been reported without coöperation. Our sincerest thanks are extended to all who have aided, in particular to Dr. W. S. McCann, Professor of Medicine, University of Rochester, who placed his records at our disposal, and to Dr. S. W. Clausen who also granted us that courtesy. Dean George H. Whipple of Rochester, University School of Medicine and Dr. Wm. B. Hawkins have been most generous in allowing us to have uncut hearts. Dr. E. C. Reifenstein, Professor of Medicine at Syracuse University College of Medicine, Dr. Charles Post, Dr. J. G. F. Hiss, and Dr. Irving Ershler also coöperated in providing histories and material. Dr. J. Howard Ferguson, Dr. Tyree Wyatt, Dr. James Wilson, and Dr. Arthur Harris are warmly thanked for providing hearts for examination. Dr. W. E. Barnett of Logansport, Indiana, Dr. Marguerite McCarthy, of Syracuse, and Dr. W. D. Paul from the service of Dr. Fred Smith of Iowa City have each provided 1 valuable case with complete data. Finally, one history, electrocardiogram and autopsy verification were obtained from the records of the late Dr. Joseph Sailer of Philadelphia. We regret that to conserve space it has been necessary to omit much of the clinical data (especially protocols for Cases 24, 25, 27, 28, 29) and in Cases 4, 24, 25, and 29, the electrocardiograms as well. These data will be supplied upon personal request.

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THE TREATMENT OF PNEUMOCOCCIC PNEUMONIA BY HYDROXYETHYLAPOCUPREINE.

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Our first clinical report[1–4] on the results of the treatment of pneumococcic pneumonia from 1935 to 1937 by hydroxyethylapocupreine was made last year. The present paper is a further analysis of the data from a similar group of cases occurring during the past year, from July 1, 1937, to June 30, 1938.

In the analysis of our mortality figures there are three facts to which we desire to refer very briefly. We are aware of their triteness. The death rate for pneumonia per 100,000 population shows that Pittsburgh has consistently a very much higher mortality than any other large city in the country. For the past 3 years it has been 161, 193 and 167, respectively. Comparative figures for most of the large cities can be noted in the City of New York Department of Health, Quarterly Bulletin. We hold no brief for the accuracy of these figures from different cities, but one would imagine that errors would be probably about the same for each city. The Pittsburgh death rate, according to this data, is frequently twice that of many of the other cities. Our material, therefore, comes from a community in which pneumonia is a severe disease. The type of human beings who make up the majority of the cases studied in any pneumonia series must be considered as having an influence on the mortality rates. In the public ward service of any large city hospital a fair percentage of the pneumonia patients present evidence of alcoholism, malnutrition and physical neglect. It is logical to expect that the mortality in pneumonia of this group will be decidedly higher than in private cases in their homes or in hospital private rooms. Our cases in the first 2 years were over 90% from the public ward and last year the figure was 81%. It is important, therefore, to keep the human element in mind when comparing statistics regarding pneumonia. Since the last week in December, 1936, we have been impressed with the frequency of postinfluenzal

pneumonia which in our cases has been a mixed infection. Strep. hæmolyticus and H. influenzæ, considered as the most frequent secondary invaders following virus infection, have been present in cultures from the sputum in from about one-half to two-thirds of our cases over this period of time, whereas in the 2 previous years these organisms were not commonly found. We believe it is almost as important from a bacteriologic point of view to culture the sputum as it is to differentiate the pneumococcus into its different types. The mixed infections undoubtedly present a changed clinical picture from pure pneumococcic pneumonia, and at autopsy they are definitely different. It is by no means always an easy matter to be certain of the influence of the Strep. hæmolyticus and H. influenzæ in any given case of pneumonia, particularly early in its course, when one finds in culture of the sputum these organisms associated with the pneumococcus. Atypical clinical courses are suggestive of more than pure pneumococcus infection. A subsequent Strep. hæmolyticus empyema would logically point to the influence of this organism on the pneumonia while delayed resolution and the Strep. hæmolyticus similarly appear to be closely related. It is our opinion from clinical observations only, that in mixed infections the results with the chemical have not been as good as when the case appeared to be a relatively pure pneumococcic infection.

Hydroxyethylapocupreine dihydrochloride was given in capsules by mouth, 15 gr. every 3 hours day and night for 3 to 5 days. In some patients, it produced nausea and occasionally vomiting. However, in only a few cases was it necessary to discontinue the chemical for this reason. It may be that in the future the base or another salt will be used by mouth instead of the dihydrochloride. For intravenous use, a monohydrochloride solution is given, each 50 cc. containing 15 gr. and this is injected into the vein every 3 hours. The monohydrochloride solution is readily made by dissolving 15 gr. (1 gm.) of the hydroxyethylapocupreine dihydrochloride in 50 cc. of distilled water (a 2% solution) and to this solution adding slowly about 2.5 cc. of normal sodium hydrate. The solution becomes milky at first but clears when the monohydrochloride stage is reached. The intravenous solution is given slowly, from 7 to 10 minutes being taken for the 50 cc. At this rate, there have been no reactions. If given rapidly, a weak rapid pulse may be noted with some fall in blood pressure. We have seen very few reactions of this kind and we feel fairly certain that their cause is carelessness due to speed in the injection of the chemical. In 3 years we have seen no evidence of visual disturbance. Thrombosis of the veins of the arm at the point of injection with the intravenous method does occur at times especially if the veins are difficult to enter, but it is less with the monochloride than with the dihydrochloride.

As in the previous 2 years, no one under the age of 15 has been

included in our analysis of treated cases. Drs. M. L. Menten and R. MacDonald will later report their results on the treatment of children from the Children's Hospital, Pittsburgh. Postoperative pulmonary conditions also have been excluded so as to avoid confusing collapse and embolism with pneumonia.

During the past year in our 149 chemically treated patients we have had 2 cases of pneumococcic empyema. Both were surgically drained, although 1 had had the hydroxyethylapocupreine injected into the pleural cavity according to the method we described in our previous paper. These cases recovered.

Two pneumococcic empyema cases that had not been chemically treated for the pneumonia, but were admitted after the empyema had developed, showed in 1 at autopsy endocarditis and empyema. The other patient was a man of 75 in whom surgical drainage was required after several injections of the chemical into the pleural cavity. He recovered. There were 3 empyemas in children, ages 6 to 9 years. Two received chemical treatment for the pneumonia while 1 had Type I serum. The last case made a prompt recovery from the empyema with intrapleural injections of the hydroxyethylapocupreine. One of the first 2 recovered with surgical drainage, but the other died from massive collapse of lung following the surgical interference. This last case had previously been given the chemical injections into the pleural sac.

There were 3 cases of Strep. hæmolyticus and 2 of Staph. aureus empyema. One of the latter followed a severe trauma but the remainder were the end results of what we considered postinfluenzal pneumonia with mixed infection. The empyemas were treated surgically, 2 recovered and 3 died; 1 death followed a severe hemorrhage from the lung almost 2 months after an apparently good recovery. The exact cause of this hemorrhage was not determined.

The small percentage of Type I pneumonia has been typical of the Pittsburgh infection in all hospitals for many years. Type II pneumonia has shown a steady increase during the past 3 years as the percentage figures 13, 16 and 32, respectively, would indicate. During the past year, this type of infection was not only the most frequent, but also showed the highest mortality. The undetermined types were cases outside of our hospital where typing had been negative with I, II, V, VII and VIII serum, but not carried further. There were 5 cases on the table showing multiple types, and in a comparatively large number, noted as unclassified, we could not establish the type of pneumococcus.

The bacteremia chart shows the important part played by Type II pneumonia in our cases of last year. This type comprised 62% of all the bacteremia cases and 59% of our Type II pneumonias had a bacteremia. In our experience, the finding of Type II pneumococcus in blood cultures rarely ever is associated with a mild infection even with low or absent colonies on the poured plates. The undetermined cases are the same as those referred to in the first table.

The data on the serum cases was kindly furnished by Dr. Philip Marks, of the Department of Public Health, Pittsburgh, and includes all serum-treated cases from our hospital. The city of Pittsburgh supplied, free and

TABLE 1.—THE RESULTS OF TYPING IN 204 CASES OF PNEUMONIA. 1937–1938.

Type.	No. of cases.	Percentage.
I	26	12.7
II	66	32.3
III	23	11.6
IV	3	1.47
V	8	3.9
VI	1	0.49
VII	8	3.9
VIII	10	4.9
IX	3	1.47
X	2	0.98
XI	1	0.49
XII	4	1.95
XIII	3	1.47
XV	1	0.49
XVI	3	1.47
XVII	1	0.49
XVIII	2	0.98
XX	2	0.98
XXII	2	0.98
XXIII	1	0.49
XXV	2	0.98
XXVIII	3	1.47
XXIX	1	0.49
XXXII	2	0.98
IV, VII, XXIX	1	0.49
V, XVI, XVIII, XXIX	1	0.49
XIII, XXI, XXVIII	1	0.49
II, XVIII	1	0.49
III, IV	1	0.49
Unclassified	14	6.85
Undetermined	7	3.43

TABLE 2.—ANALYSIS OF BACTEREMIA CASES. 1937–1938.
(176 cases had daily blood cultures taken during the febrile period of the disease; of these, 62 were positive, 35.2%.)

Type.	No. of bacteremia cases.	Percentage.
I	4	6.45
II	39	62.9
III	8	12.9
V	3	4.84
VII	1	1.61
VIII	1	1.61
XII	1	1.61
XX	1	1.61
XXV	2	3.22
XXXII	1	1.61
Undetermined	1	1.61

Incidence of Bacteremia According to Type.

Type.	No. of cases.	Bacteremia cases.	Percentage.
I	26	4	15.4
II	66	39	59.1
III	23	8	34.7
V	8	3	37.6
VII	8	1	12.5
VIII	10	1	10.0
XII	4	1	25.0
XX	2	1	50.0
XXV	2	2	100.0
XXXII	2	1	50.0
Undetermined	7	1	14.2

liberally, specific serum for Types I, II, V, VII, VIII and XIV to all cases where the disease was not beyond the end of the third day. The first two items in Table 3 have included all cases in the treated and non-treated groups even if the patient died a few minutes after admission to the hospital in the non-treated group, or in the treated group if only a single dose of the chemical was given. We feel that the "two days in hospital" figures give a more accurate estimation on which to draw conclusions, although the results in the two groups relatively are almost the same. The "no specific treatment" cases, with few exceptions, entered the hospital after the fourth day of the disease.

TABLE 3.—ANALYSIS OF PNEUMONIA CASES.

	No. of cases. 1937–1938.	Percentage died.
No specific treatment	41	56.2
Hydroxyethylapocupreine (any) . .	167	25.7
No specific treatment (in hosp. 2+ days)	30	40.0
Hydroxyethylapocupreine (2+ days) .	149	17.4
Specific serum . .	285	22.0

There were 24 additional chemically treated cases on whom blood cultures were not made; nearly all of these cases were at home, but a few were in other hospitals. Blood culture data on the serum-treated cases of the city of Pittsburgh series were unfortunately not available for comparison with our material in Table 4.

TABLE 4.

1937-1938.

	No of cases.	Bacteremic Cases	Percentage died.
No specific treatment	8		87.5
Hydroxyethylapocupreine	36		61.1
		Non-bacteremic Cases	
No specific treatment	21		23.8
Hydroxyethylapocupreine	89		3.3

Table 5 indicates that with one exception all of the recovered bacteremic cases were of the first three types and as Type II represented 62% of our bacteremias, it is logical that most of the recoveries were of this infection. All of the non-bacteremic Type II cases (15) recovered.

To Table 7 of our previous paper for the years 1936–37 should be added 4 more cases with bacteremia which recovered. These cases occurred in the months of May and June; the table as published was for 10 months only. The types were I, II, VII and an undetermined higher type. The highest

colony count was 44 in Type II, 1 in Type VII and pneumococci in the broth only in the other two types. In the past 3 years there have been 37 cases with bacteremia which have recovered, and in 8 of this number, the colony count has been 33 or more. We have not seen a recovery in a non-specifically treated case (serum or chemical) with a bacteremia above 15 colonies per c.mm. of blood over a period of 8 years when blood cultures have been taken daily or very frequently during the febrile course of the pneumonia. We are aware that others have described such cases and we do not doubt their occurrence, but they must be very infrequent.

TABLE 5.—RECOVERED CASES WITH BACTEREMIA. 1937–1938.

Sex.	Age.	Type.	No. of positive cultures.	Highest colony count.
M.	39	I	2	0
M.	20	II	2	0
M.	47	II	2	3
M.	41	II	2	1
M.	54	II	4	96
M.	45	II	1	4
M.	39	II	3	33
M.	32	II	2	0
F.	58	II	1	0
M.	40 (?)	II	1	0
M.	41	II	1	0
M.	59	III	4	187
F.	35	III	2	0
M.	55	XXV	2	0

TABLE 6.—COMPARISON OF SERUM AND CHEMICALLY TREATED CASES.

	No. of cases.	1937–1938.	Percentage died.
Type I.			
Serum	90		13.3
Hydroxyethylapocupreine	16		12.5
Type II.			
Serum	124		32.2
Hydroxyethylapocupreine	39		35.9
No specific treatment	12		58.3
Type III.			
Hydroxyethylapocupreine	18		22.4
Types IV,V,VII,VIII.			
Serum	70		15.7
Hydroxyethylapocupreine	24		16.6

In comparing the results of serum-treated cases in Pittsburgh as reported by the Department of Health with our chemically treated cases of the same types during the same period of time one sees very little difference.

The combining of serum and chemical, particularly in Type II, will probably be tried next year if the infection retains the virulence it appeared to possess during the past year. This could also apply to the other types for which there is an available specific serum. Experimentally, there is considerable evidence in the past to show that optochin increased the protective power of specific serum and we have noted the same with hydroxyethylapocupreine. The reader is referred to White's[5] excellent book on *The Biology of Pneumococcus* for the discussion of this phase of the problem.

TABLE 7.—COMPARISON OF HOME AND HOSPITAL CASES TREATED WITH SERUM AND CHEMICAL.

	No. of cases.	1937–1938.	Percentage died.
Specific serum (home)	126		13
Specific serum (hospital) . . .	159		29
Hydroxyethylapocupreine (home)	27		8
Hydroxyethylapocupreine (hospital)	122		19

This chart shows, both for serum and chemical, the difference between hospital and home mortality. Our hospital cases treated with chemical were almost all public ward patients, and in our opinion their poorer human fiber accounts to a great extent for the difference in mortality.

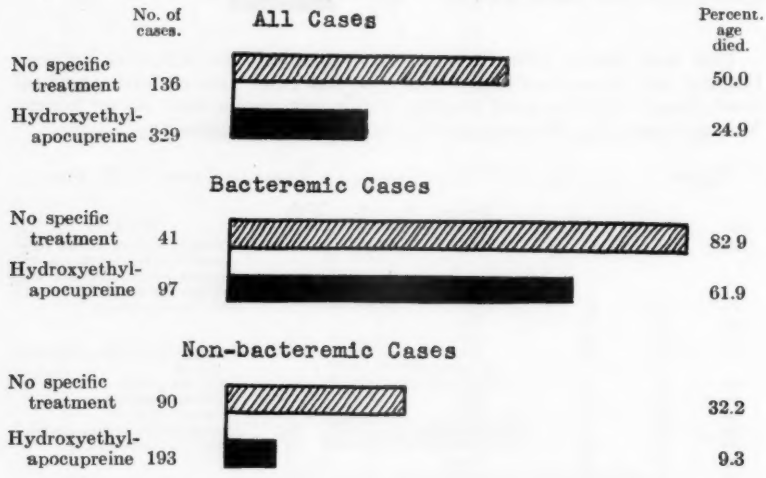
TABLE 8.—ANALYSIS OF FATAL CHEMICALLY TREATED CASES. 1937–1938.

Age.	Sex.	Type.	Bacteremia.	No. pos. cultures.	High count.	Remarks.
46	M.	I	Pos.	3	0	Autopsy, diffuse active caseous bronchopneumonia, left upper lobe; lower left lobe Type I pneumonia.
35	F.	I	Neg.	..	..	Acute encephalitis.
33	M.	II	Pos.	3	*	
37	M.	II	Pos.	1	15	
37	M.	II	Pos.	5	600	Autopsy. postinfluenzal pneumonia.
39	M.	II	Pos.	3	94	Delirium tremens.
54	M.	II	Pos.	5	*	Delirium tremens.
43	M.	II	Pos.	1	0	Delirium tremens.
22	M.	II	Pos.	12	26	Endocarditis, pneumococcic.
35	M.	II	Pos.	3	11	Delirium tremens.
34	M.	II	Pos.	5	3	
19	M.	II	Pos.	5	3189	
29	M.	II	Pos.	1	0	Autopsy, acute encephalitis, postinfluenzal pneumonia.
28	M.	II	Pos.	1	1	
29	F.	II	Pos.	2	0	
39	M.	II	Pos.	5	4500	
48	M.	III	Pos.	2	9	Autopsy, acute coronary thrombosis.
45	F.	III	Neg.	..	..	Acute coronary thrombosis—clinical evidence only.
74	M.	III	Pos.	1	0	
70 (?)	M.	III	Not taken			
41	M.	V	Pos.	3	3800	
31	M.	V	Pos.	5	98	
21	M.	VII	Neg.	..	..	General peritonitis, probable ruptured appendix.
72	F.	VII	Pos.	3	7	
35	M.	XXXII	Pos.	4	1	Acute encephalitis.
38	F.	(undetermined)	Pos.	2	0	

* Innumerable.

Dr. Permar demonstrated during the past year fairly frequently at the autopsy table postinfluenzal pneumonia which is always a mixed infection. There were a number of examples of this infection among the "no specific treatment" cases which are naturally not in the above list. Only those cases coming to autopsy have been considered as postinfluenzal pneumonia in the above analysis, although from the clinical and bacteriologic examination of the sputum there were several more of this type. Pneumococcus was present in all. Acute encephalitis in 2 instances was the diagnosis by clinical and spinal fluid examination. In the third case, autopsy confirmed the clinical diagnosis. It was seen several times in the "no specific treatment" group. We did not have a case of pneumococcus meningitis during the year. In the peritonitis case, the febrile course of the pneumonia had dropped to normal by lysis. This was followed rapidly in the course of 24 hours by typical signs of general peritonitis. Appendiceal origin was considered most likely by the surgical department and by us. Operation, on account of the state of the patient, was considered inadvisable and an autopsy was not obtainable. Several other autopsies were done in this group but the findings were typical of pneumococcic pneumonia and are, therefore, not noteworthy.

TABLE 9.—SUMMARY, 3 YEARS, 1935–1938.



The "no specific treatment" cases as in the other tables were, with few exceptions, ill at least 4 days on admission. In some of the hydroxyethylapocupreine cases this year treatment began on the fourth day and a few even later.

It will be noted in Table 10 that the number of cases on the third day of disease when chemical treatment began was much larger than on any of the other days. We purposely withheld the chemical until the third day in many instances. In our hospital work we do not see very many admissions on the first day of disease. Cases appearing within 10 to 12 hours after onset were treated, otherwise the chemical was withheld until 2½ days after the onset. In our first clinical report we noted the low mortality in cases when treatment began on the third day and it was

to test this observation further that we withheld treatment. Table 10 still shows the lower mortality of the third day cases, but we believe much larger numbers should be analyzed to prove the observation prior to attempting to explain the fact. There have been a few cases this year which have not been included among the treated group where chemical has been given within a few minutes to 2 to 4 hours after the initial chill. These patients were not in the hospital so that Roentgen rays were not taken. They were all adults and 2 or 3 had bloody sputum in which pneumococci were found. The temperature promptly came down inside of 24 hours and remained normal. No typical physical signs ever developed so they were not included as pneumonia cases. We noted a few cases of this type last year. They are likely only seen in private practice, but undoubtedly in the future this group may form a very interesting class to watch. The ideal time to use the chemical may be immediately following the chill. This would apply, therefore, almost entirely to the practitioner of medicine rather than to the hospital physician.

TABLE 10.—MORTALITY ACCORDING TO DAY OF DISEASE WHEN FIRST TREATED.

	No. of cases.	1935–1938.	Percentage died.
First day	67		28.4
Second day	53		35.9
Third day	128		17.9
Fourth day	50		38.0
Fifth +day	25		27.9

Conclusions. 1. The mortality figure in pneumococcic pneumonia in adults during the past year has been greatly reduced in those cases which received hydroxyethylapocupreine.

2. In comparing the mortality figures of our chemically treated cases, which were, of course, smaller in number, with the serum-treated cases in Pittsburgh for the same types of pneumonia, during the same period of time, almost identical results were observed.

3. Hydroxyethylapocupreine has shown no evidence of disturbing vision.

The authors wish to express their thanks to Dr. H. H. Permar for his help during the past year.

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THE BLOOD PLATELET COUNT IN RELATION TO THE MENSTRUAL CYCLE IN NORMAL WOMEN.

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Cases of thrombocytopenic purpura occurring periodically with menstruation have been recorded, especially by Minot.[16] In these individuals the blood platelets decreased rapidly to very low numbers near the onset of menstruation and returned to normal values during the intermenstrual period. In chronic thrombocytopenic purpura a further decrease of the platelets may occur at the time of menstruation accompanied by an exacerbation of symptoms. Denisova-Suscevska[8] observed such a case for 22 years. These observations suggest that an abnormal exaggeration of a physiologic cyclic process associated with menstruation may be responsible for the decrease of platelets.

The present investigations were carried out in an effort to determine if there was any regular variation in the number of blood platelets during the menstrual cycle in normal women and to evaluate the conflicting reports on this subject. The problem has received little study and the investigators who have reported a regular variation are not agreed on the type or amount of change, nor during which part of the menstrual cycle it occurs.

Pfieffer and Hoff[18] were the first to report a distinct decrease in the number of blood platelets with the onset of menstruation. Henning,[11] Francesco,[9] Sakai,[19] Benhamon and Nouchy,[4] and Kato[13] have confirmed these observations. Brinck and Patrunky[5] demonstrated a decrease in platelets during the premenstrual period in normal subjects. Dameshek[7] recorded a fairly constant intermenstrual figure, varying with the individual subject, but with the appearance of the menses he always observed a sudden and marked rise in the blood platelet count. Hirsch and Hartmann,[12] Denisova-Suscevaka,[8] and Morse[17] were unable to demonstrate any cyclic change in the number of blood platelets in normal women.

While the present investigations were in progress, Genell[10] reported observations on the variations in the number of blood platelets during the menstrual cycle. The data are much larger and more convincing than any previously recorded, although only average values for a group of 38 women are given. Genell concluded that the platelets varied in a regular manner which was characterized by the occurrence of the lowest values on the first and second menstrual days, a subsequent rise which reached a peak after several days, and later a premenstrual decrease.

Methods. Tocantins[21a] has recently presented an excellent review of the technical methods for the enumeration of blood platelets and states that in experienced hands direct methods give greater accuracy than indirect ones. When each step is standardized and the manipulative procedure coördinated most of the objections raised against the use of the direct method are overcome. In the present study, the number of blood platelets were determined by direct counts on capillary blood with the aid of an isotonic diluting fluid containing a stain and anticoagulant. The stain is not essential.

The dilating fluid used was with slight changes Edwards' modification of Buckman[6] and Hallisey's fluid. Its composition was 8 gm. of cane sugar, 2 gm. of sodium citrate and 0.04 gm. of brilliant cresyl blue made up to 100 cc. with distilled water. All glassware used was scrupulously clean. The sodium citrate and sugar were dissolved in a portion of the distilled water, filtered and placed in a volumetric flask. The stain was ground in a mortar and transferred into the flask by washing. This solution was shaken thoroughly and allowed to stand 6 hours with frequent agitation. It was then made up to volume with distilled water. The solution was centrifuged at 2000 revolutions per minute for 30 minutes and pipetted into a clean glass-stoppered bottle. It was stored in an ice-box with a temperature of from 5° to 10° C. This solution can be kept in this manner for many months and under these conditions is bacteriostatic. Blank counts from time to time were never over 5000 platelet-like bodies per c.mm. A small amount of solution was filtered each day as needed. The unused portion was never returned to the stock bottle.

Freely flowing capillary blood was obtained from a deep stab wound in the ear lobe with a sharp No. 8 Keith's abdominal surgical needle fixed in a cork. If blood for other purposes was obtained from the same puncture the sample for platelet determination was always taken first. The blood was drawn to the 0.5 mark in a certified red blood cell counting pipet and diluted immediately to the 101 mark with the platelet diluting fluid. The pipet was sealed with a rubber band and shaken immediately in an automatic shaker for 5 minutes. A counting chamber with improved Neubauer ruling certified by the United States Bureau of Standards was then filled. The preparation was allowed to stand in a moist chamber for 15 minutes before counting the platelets. The number of platelets per c.mm. was calculated by counting those present in 2 sq. mm. and multiplying by 1000. A high dry objective with magnification of × 400 was used. The simplest areas in which to count the platelets are the squares to the right and left of the finely ruled center area. The distribution was checked each time by comparing the values for each of the sq. mm. spaces. The fine adjustment of the microscope was used continually to obtain the necessary critical focusing. Only characteristic highly refractile forms of round, oval or comma shape (if seen in profile), varying in size from 1 to 5 micra, were counted. Irregularly shaped débris, bacteria, fat globules and other minute objects could be readily eliminated by the experienced eye.

Experimental. The average of all platelet counts done on normal women in this laboratory by the author in the past 2 years, using the above method, was 265,000 per c.mm. The normal range in women is extremely wide as will be shown later. The average for normal males was approximately 300,000 platelets per c.mm., with a range of from 250,000 to 400,000.

The present investigation required repeated observations on the number of blood platelets making it necessary for the counts to be made on capillary blood. However, a preliminary study was made

on 8 women to compare the numbers of platelets in venous and capillary blood. When venous and capillary blood was taken simultaneously, 126 determinations showed that the values for venous blood were persistently higher than those for capillary blood. The platelet counts on venous blood averaged 15% more than those on capillary blood. This difference has also been reported by Tocantins.[21b] However, the difference was consistent and therefore direct platelet counts on capillary blood obtained from the ear were satisfactory for a statistical study.

A total of 1034 blood platelet counts were made on 13 normal white women. The subjects were unmarried laboratory technicians, ranging in age from 19 to 40 years. All had a normal menstrual cycle from 25 to 31 days in length and normal menses of 4 to 5 days' duration. There was no serious illness in the group during the period of observations and none showed purpuric manifestations or presented abnormal bleeding. The number of blood platelets were observed during a total of 82 menstrual cycles. No subject was followed for less than 3 complete cycles. No definite seasonal variation in the blood platelet level was noted, although this study was begun in October, 1936, and terminated 1 year later.

The subjects had very little dysmenorrhea. Seven individuals took no drugs whatsoever and 6 occasionally took 5 to 15 grains of aspirin the first or second day of the period. It should be emphasized that no drugs were taken before the onset of the menstrual flow.

All the counts were done at about the same time of day (10 A.M.). The factors of food and exercise which might influence the counts were fairly constant at this hour. During the early part of the investigation platelet counts were occasionally performed on the same subject twice daily. However, it was soon found that there was rarely any significant difference between the morning and afternoon values. In compiling the data if there was more than one determination on any particular day the average was taken. Throughout the 82 menstrual cycles there was an average of one determination every other day.

Seventy-five per cent of the blood platelet counts were done by the author and the remainder by an experienced technician. It was found that the results obtained by one individual checked with those obtained by the other within a range of 20,000 platelets per c.mm. Based on the average of 265,000 platelets per c.mm., this admits a technical error of approximately from +4% to −4%.

The 1034 blood platelet counts on 13 normal women, during a total of 82 menstrual cycles are recorded in Figure 1. Each dot represents a platelet count which is plotted in relation to the day of onset of the menses thus enabling the data on various subjects to be superimposed. Mean values were calculated for each day of the cycle and a line drawn connecting these points on the chart.

The mean values and the median values are almost identical. The average daily blood platelet count shows a variation in relation to the menstrual cycle. The average platelet count is at its lowest level on the day of onset of the menses (220,000 per c.mm.). Following this there is a rapid rise to about 275,000 per c.mm. The number remains rather constant at this level until 2 weeks before the onset of the next period. During the 2 weeks premenstrual period there is a slow progressive decrease in the number of blood platelets.*

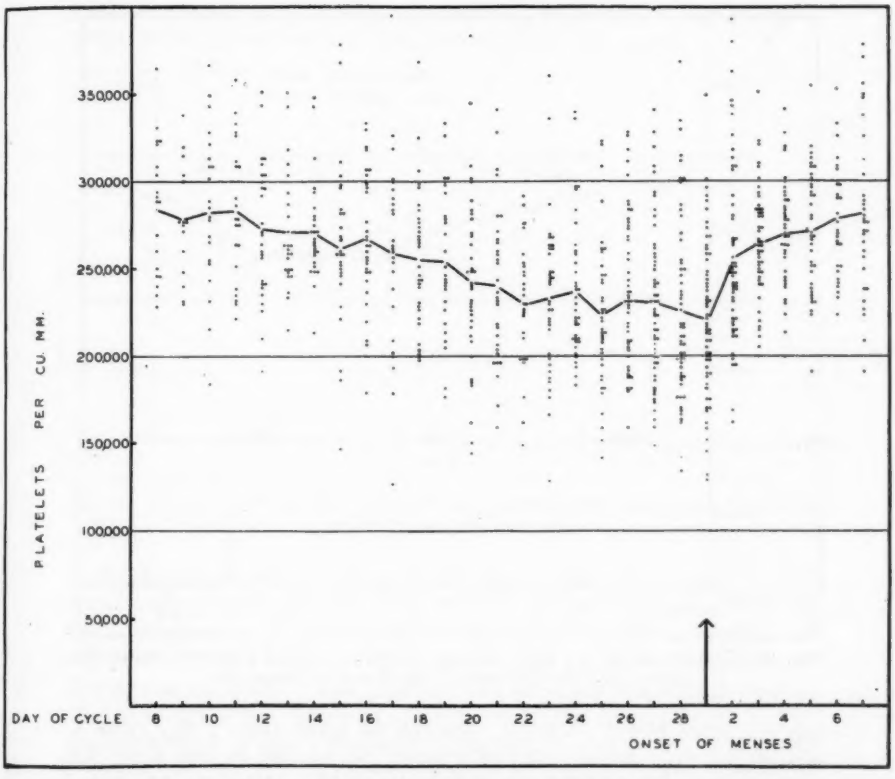

FIG. 1.—Blood platelet counts during 82 menstrual cycles in 13 normal women plotted in relation to a "28-day" menstrual cycle. (.————. average.)

The average number of blood platelets in relation to the menstrual cycle in these cases and in Genell's[10] cases are shown in Figure 2. Genell used Kristenson's[14] method for the enumeration of the platelets which is similar to the method used in the present study. These two groups show approximately the same variation

* A regression line was fitted to this slope and proved to be significant by the (t) test.

in the number of blood platelets in relation to the menstrual cycle. The major discrepancies lie in the lower figures obtained by Genell on the first and second days of menstruation and the more prolonged postmenstrual rise.

An analysis of the platelet counts for each of the 13 women studied or for each of the 82 menstrual cycles studied showed significant variations from the average data for the entire group. Variations greater than the range of technical error (±4%), took place only during the *premenstrual phase*. It has been assumed, for analytical purposes, that a minimum variation of 60,000 platelets

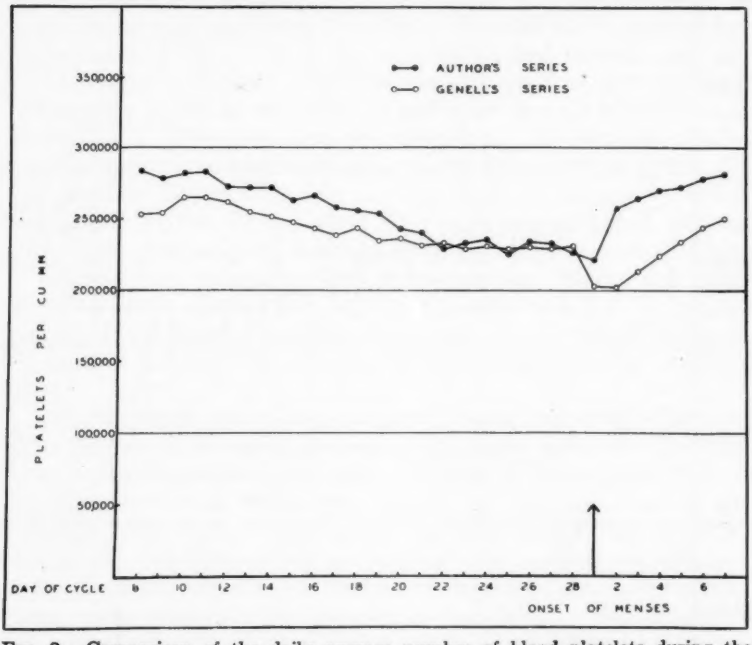

FIG. 2.—Comparison of the daily average number of blood platelets during the menstrual cycle observed by Genell and by the author.

per c.mm. of blood (±12%), checked on more than 1 day, was a significant fluctuation. On this basis the results in the total 82 menstrual cycles studied may be summarized as follows: 57 of the cycles showed a premenstrual decrease in the number of blood platelets, 22 showed no premenstrual change and 3 showed a premenstrual increase. All instances of a premenstrual rise in the number of platelets occurred in 1 individual. Seven subjects repeatedly showed a premenstrual decrease in the number of blood platelets and 5 only occasionally. In 1 subject a premenstrual decrease was suggested with alternate menstrual cycles. Figure 3 shows the rhythmical fluctuations in the blood platelet count during four consecutive menstrual cycles in 1 subject. The data in this

figure are typical of that obtained for all the individuals consistently showing a premenstrual decrease of the platelets. Other cases occasionally showed a more rapid and marked premenstrual decrease in the platelets (*e. g.*, from 350,000 to 150,000 per c.mm.) but such changes were exceptions rather than the rule.

Disregarding the 3 instances of a premenstrual increase in the blood platelets, which occurred only occasionally in 1 individual, and assuming that a decrease and no change are equally likely, the expected number of cycles showing a premenstrual decrease is 39.5. The observed number was 57 and the deviation from the mean is therefore 17.5. The probability of a chance deviation as great as the one observed is approximately 1 in 10,000.

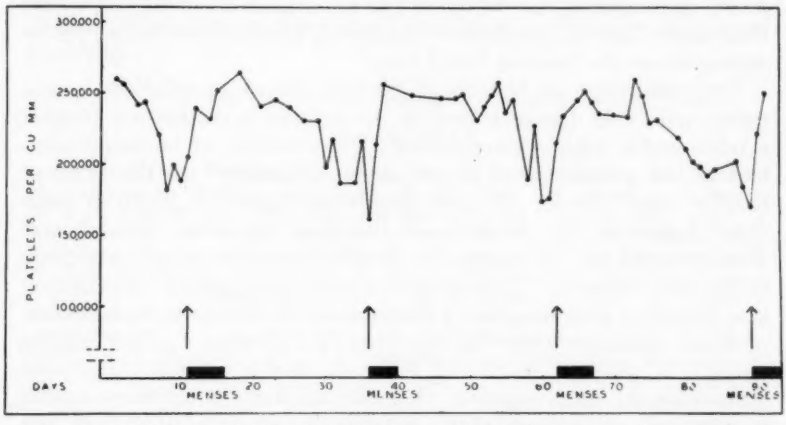

FIG. 3.—Variations in the blood platelet count during four consecutive menstrual cycles in a normal woman.

White blood cell counts and differential white blood cell counts were made simultaneously with blood platelet determinations on these subjects on 122 occasions. The white blood cell count and differential count failed to show any regular variation in relation to the menstrual cycle. The reticulocytes were not abnormally few at the time when the platelet counts were at the lowest levels. The bleeding time (Duke's method) occasionally seemed to be slightly increased during the premenstrual period. However, the method is entirely inadequate for measuring slight changes.

Discussion. The lack of agreement among earlier investigators in regard to a regular variation in the number of blood platelets in relation to the menstrual cycle in normal women may be explained by the limited observations and the fact that all individuals do not respond in an identical manner. This is substantiated by the fact that Genell's[10] and the present studies give more data than previous reports and the results obtained were entirely similar.

The mechanism producing the usual regular variation in the blood platelet count in relation to the menstrual cycle is unexplained.

Genell believed that the postmenstrual rise was an increase above the normal platelet level due to absorption of necrosed endometrium.

It has long been known that hemorrhage usually causes an increase of blood platelets. The amount of blood loss necessary to cause a rise in the platelet count is not known. It probably varies tremendously in different individuals. Recent studies (Leverton and Roberts,[15] Widdowson and McCance,[22] and Barer, Fowler and Baldridge[3]) have shown the average amount of blood lost with each menstrual period is a little less than 50 cc. We removed 15 cc. of blood daily for 5 days from a normal male and from a normal female during the intermenstrual period without any change in the blood platelets. Pfeiffer and Hoff[18] bled 2 men 50 cc. daily for 5 or 6 days without alteration of the blood platelet level. It would thus seem that the postmenstrual rise in blood platelets cannot be explained on the basis of blood loss.

The variations in the blood platelet count in relation to the menstrual cycle demonstrated in the present investigation suggest a relationship with sex hormones. The question of hormonal control of the platelet level is not new. Schröder,[20] on the basis of clinical observations, felt that female sex hormones given in large doses inhibited the function of the bone marrow. Zondek and Kaatz[23] could find no change in the platelet count in patients given estrin and progestin. These observations were limited. Benhamon and Nouchy[4] were unable to demonstrate a change in the number of blood platelets after the injection of folliculin. Sakai[19] claims there is a stimulation of the function of the reticulo-endothelial system during menstruation. Hirsch and Hartmann[12] were unable to produce alterations in the platelet count in rabbits with the injection of "ovo- and luteo-glandol." Bankow[2] produced a reduction in the number of blood platelets in white rats after castration. Pfeiffer and Hoff[18] theorize that the corpus luteum hormone influences the spleen so as to prevent out-pouring of platelets. Recently Arnold, Holtz, and Marx[1] have reported the production of an experimental Werlhof's disease in dogs by the administration of large doses of Progynon B-oleosum or the ovarian panhormone of Henning. If the drug was stopped early in the disease, the animals recovered. If the drug was continued, the thrombopenia persisted and the animals died from hemorrhages.

The significance of a premenstrual decrease in the platelets is problematical. Some investigators prefer to look upon it as a periodic latent hemorrhagic diathesis. It may be one of several factors that has led to the general impression that certain women bruise more easily towards their menstrual period. It may be a factor in certain cases of so-called "vicarious" menstruation where misplaced endometrium cannot be demonstrated. Cases of intermittent idiopathic thrombocytopenic purpura related to menstruation may be an exaggeration of this apparently physiologic cyclic process.

Conclusions. 1. The determination of the number of platelets by direct counts on capillary or venous blood, with the aid of a satisfactory diluting fluid, is a useful and accurate method. Platelet counts on venous blood average 15% higher than those on capillary blood.

2. The average number of blood platelets in 13 normal women observed during a total of 82 menstrual cycles varied in a regular manner in relation to the menstrual cycle. This change was characterized by a slow progressive decrease during the 14 days prior to menstruation and a rapid increase soon after the onset of the menses. In individual cases there was usually either a slow progressive premenstrual decrease or a rapid decrease immediately before menstruation. In a few instances there was little or no cyclic change in the platelet count and rarely a premenstrual increase occurred.

The author gratefully acknowledges the assistance of Miss Elizabeth King.

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THE PRESENT INCIDENCE OF TRICHINELLA SPIRALIS IN MAN AS DETERMINED BY A STUDY OF 1060 UNSELECTED AUTOPSIES IN ST. LOUIS HOSPITALS.*

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All life is apparently subject to parasitism and man is no exception to this general rule, for he has suffered the torment of various

* The author is indebted to Paul A. Wheeler, M.D., Resident Pathologist, St. Louis City Hospital, for his assistance in obtaining material for this study.

parasites from the most ancient times to the present day. It has been claimed that the Mosaic injunction regarding pork was due, in some measure at least, to an infestation of the swine of that period with Trichinella spiralis. Be this as it may, the first description of this parasitic worm appeared only a little over a century ago.

Tiedemann, in 1822, probably saw the calcified larval forms of the Trichinella spiralis in the muscle tissue of his cadavers. He encountered this condition so often, however, that he regarded the calcified flecks in the muscles as mere "pathological curios" and of no practical importance. Thirteen years later (1835), James Paget,[7] then a medical student, saw these calcified bodies in the dissecting room material at St. Bartholomew's Hospital. He examined them under the microscope of Robert Brown, the botanist at the British Museum, and discovered that these white specks in the muscles represented a calcified capsule enclosing a coiled up roundworm. His friend and teacher, Richard Owen, reported the discovery to the Zoölogical Society and named the worm Trichina spiralis. Due to confusion with another parasite the term was later changed to Trichinella spiralis. Zenker[16] was the first to recognize the condition of trichinosis (*i. e.*, trichiniasis) in a girl 19 years of age, who died of what was thought to have been typhoid fever. He found the adult trichinellæ in the intestine and the larvæ in the muscles but not the lesion of typhoid. Virchow[13] and Leuckart,[4] working independently demonstrated the relation of the adult intestinal worm to the larval form in the muscles by feeding the latter to animals. Leidy,[3] of Philadelphia, in 1847, found the Trichinella spiralis in pork which brought to light the importance of this parasite as a public health problem.

The main purpose of the present study was to determine as accurately as possible the extent to which man is, at the present time, infested with Trichinella spiralis.

Method. Muscle tissue from 1060 unselected autopsies at Barnes and St. Louis City Hospitals was examined for trichinella larvæ. All of the subjects were over 15 years of age and had died during hospitalization from some disease other than trichiniasis. At autopsy, generous samples of the muscles of election for trichinella, namely, the diaphragm, intercostals, pectorals and recti, were removed and stored on ice in a fresh state if the examination could not be carried out at once. From this material, compression sections were prepared by squeezing thin slices of muscle tissue between two pieces of plate glass in a compression frame (Fig. 2). These fresh unfixed and unstained preparations were then examined microscopically in a methodical manner so that every field in a specimen came into view. Over 12,000 examinations of this type were made during the course of this study in addition to an examination of the usual stained histologic sections (Fig. 3).

Out of 1060 autopsies upon the bodies of individuals never suspected of having trichiniasis during life, 163 (15.37%) nevertheless showed the presence of trichinella larvæ in the muscles. The para-

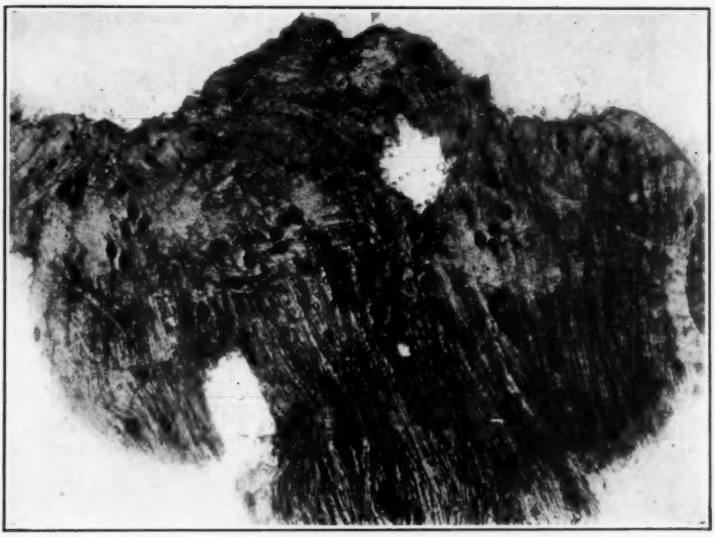

FIG. 1.—Specimen of unstained infested human muscle in compression frame, showing numerous calcified trichinella larvæ. (× 10.)

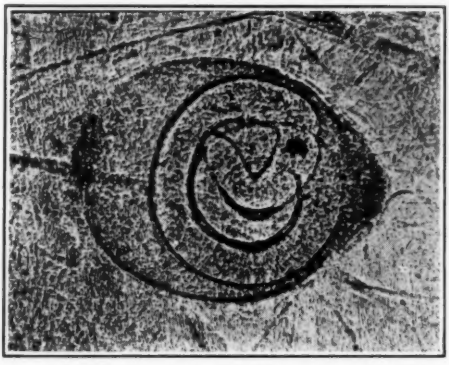

FIG. 2.—Coiled larva within capsule. The dark areas at either end represent beginning calcification. Unstained compression preparation. (× 200.)

FIG. 3.—Histologic section of encapsulated larva stained with hematoxylin and eosin. (× 200.)

sites were apparently dead in 95% of the cases. In 2 subjects, one 17 and the other 19 years of age, the trichinellæ were completely calcified. On the other hand, in some cases the parasites moved vigorously and often continued to show signs of life for 1 to 6 days after the muscle had been removed. The presence of live parasites was also demonstrated by feeding infested muscle to white rats and recovering the larval forms at the end of 40 days. By these means 5% of the positive cases were shown to contain viable parasites.

TABLE 1.—DEGREE OF INFESTATION OF 163 CASES SHOWING TRICHINELLA SPIRALIS.

Degree.	No. of cases.	Per cent.
Heavy (numerous parasites in every microscopic field*)	18	11.0
Moderate (averaging 1 parasite per 10 fields)	80	49.1
Light (1 or 2 parasites in 50 fields)	55	33.7
Slight (a few found after long search)	10	6.1

* A low-power microscopic field was obtained with a 16 mm. objective and 5× ocular.

The degree of infestation was estimated by comparing the relative number of parasites found in the different cases.

The age of distribution among the 163 cases of infestation is shown in Table 2.

TABLE 2.—AGE DISTRIBUTION AMONG 163 CASES OF TRICHINELLA INFESTATION.

Age group, yrs.	No. of cases.	Per cent.
15 to 30	16	9.2
21 to 50	46	28.0
50 and up	101	61.9

The youngest member of the group was 17 years of age and the oldest 85. Since this is a condition in which chance contact with the parasite determines infestation, it is to be expected that the largest number of positive cases will be found in the higher age groups.

The relation of occupation to infestation is summarized in Table 3. No significant association with any line of work is however apparent.

TABLE 3.—OCCUPATION OF 163 CASES OF TRICHINELLA INFESTATION.

Occupation.	No. of cases.	Per cent.
Industrialists	52	35.0
Agriculturists	37	25.0
Professional	30	20.0
Business	30	20.0

The distribution according to sex showed almost twice as many males to be infested as females. This is of no significance because in the entire group of 1060 cases studied the males outnumbered the females by almost 2 to 1.

The number of foreign-born individuals in the group studied was small so that no definite correlation is evident between the rate of infestation and nationality.

TABLE 4.—INCIDENCE OF INFESTATION DURING THE PAST 50 YEARS.

Author.	Date.	City.	No. of examinations.	No. of positive.	Per cent.
Glazier[1]	1881	New York City	150	3	2.0
	1881	Newark, N. J.	100	1	1.0
	1881	Philadelphia	40	1	2.5
Whelpley[14]	1891	St. Louis	20	1	5.0
Thornbury[12]	1894	Buffalo	21	3	14.3
Osler[6]	1898	Baltimore and other cities	1000	6	0.6
Williams[15]	1901	Buffalo, Philadelphia, Baltimore and Denver	505	27	5.3
Total for 20-year period 1881 to 1901			1836	42	2.3
Simonds[11]	1910	St. Louis	100	2	2.0
Queen[8]	1931	Rochester, N. Y., and Boston	402	75	18.7
Riley and Scheifley[9]	1934	Minneapolis	167	30	18.0
McNaught and Anderson[5]	1936	San Francisco	200	48	24.0
Hinman[2]	1936	New Orleans	200	7	3.5
Pote	1937	St. Louis	1060	163	15.4
Total for past 27 years			2129	325	15.3

Recent reports have shown a much higher percentage of infestation than the older studies had indicated. During the 20-year period from 1881 to 1901, examinations were made by different investigators on muscle tissue obtained from 1836 autopsies, and only 42 of these were found to be infested (2.28%). During the past 27 years, the number of cases examined was 2129, of which 325 were found to be infested (15.26%). Table 4 summarizes most of the studies made in the United States since 1881.

Discussion. From the publication of Queen, Riley, McNaught and Anderson, as well as the series here reported, it would appear that the incidence of trichinella infestation has greatly increased during the last decade. In 1931, Queen found the infestation rate to be 18.6%. He did not employ the usual compression method with direct microscopic observations, but digested 50 gm. of muscle tissue and detected the parasites in the sediment after digestion. McNaught and Anderson, employing the same technique, reported an infestation of 24%. Hinman digested only 10 gm. of muscle from each case and found 3.5% positive. The increased incidence of Trichinella spiralis in man reported since 1931 cannot be attributed to the use of the newer method of digestion. Employing the older technique of microscopic examination of compressed muscle, Riley and Scheipley found 17.9% of specimens positive and the

author's series showed 15.3%. The results obtained by the two methods are close enough to indicate that either technique when properly employed is entirely adequate. The lower percentage of positive results in the earlier reports may have been due, in part at least, to the fact that the number of compression specimens examined was not large enough to detect slight degrees of infestation.

It has often been observed that a severe degree of infestation may exist without related clinical symptoms and in individuals whose history records no incident which might be interpreted as an attack of trichiniasis. Such was the case in each of the 163 positive observations made in this series. The heaviest degree of infestation was in a woman, aged 84, who died as the result of a fracture of the neck of the femur.

During the last 5 years while this investigation has been in progress, only 7 cases of trichiniasis have been reported to the health department in this area. All of these cases have been personally investigated, and it was found that 2 could be definitely accepted, while in the remaining 5 the diagnosis was questionable. This is in agreement with the absence of a clinical history of trichiniasis in practically all of the reported instances of infestation observed at autopsy. A critical study of the clinical history of each of the 163 positive cases in this series reveals that the infestation neither seriously affected the health of the individual nor influenced the course of the terminal illness.

It is disconcerting to realize that at least 15% of the adult urban population is probably infested with Trichinella spiralis, in spite of the emphasis which has been placed upon meat inspection during the past 40 years. As the result of a long experience with meat inspection, the author is of the opinion that the least likely source of the parasite is pork products prepared under Federal or adequate Municipal supervision. The incidence of infestation in hog carcasses prepared under Federal supervision in this area is extremely low. Examination of muscle tissue from 1500 carcasses prepared under such supervision during the last 15 years showed only 0.8% to be positive. In packing-houses operated under Federal supervision, all pork products which are apt to be consumed without cooking are processed to destroy the trichinella. About 50% of pork products go to the consumer in the raw state to be cooked before eating.

It has been adequately demonstrated that no practical method of meat inspection can protect the consumer from the possibility of contracting trichiniasis if unprocessed products are not thoroughly cooked. Studies in Germany[10] have shown that about 32% of the cases of trichiniasis occurring between 1881 and 1898 were due to pork products which had been examined microscopically and reported uninfested.

The most frequent source of trichinella in the author's opinion is the unprocessed pork products, especially summer sausage, prepared without supervision in small local slaughter-houses or on farms. Several recent outbreaks of trichiniasis have been traced to such sources.

In the end the final responsibility for the prevention of trichiniasis rests with the consumer, who should be admonished to avoid pork products not prepared under adequate supervision and warned to thoroughly cook all pork.

Summary. Muscle tissue from 1060 unselected autopsies were trichinous to the extent of 15.4%. There had been no symptoms suggesting trichinella infestation.

Ninety-five per cent of the infestations were dead, calcified and more or less disintegrated; 5% were demonstrated to be alive by feeding the infested material to rats and recovering live trichinella larvæ.

Very heavy infestations were to be observed where the individual gave a history of having always enjoyed good health. In 1 patient, dying at the age of 84, as the result of an accident, autopsy did not show that the infestation had contributed to the cause of death.

In 1500 hog carcasses examined for trichinella, 0.8% were found to be infested, which gives rise to the question whether man is getting all of his trichinella infestation from pork. It may be concluded that man's infestation comes from pork derived from the small packing plants, which are not supervised by meat inspection services. It is to be noted that the infestations that sporadically occur are from pork from the establishments not under Federal inspection.

Conclusions. It can be very definitely concluded that the Trichinella spiralis infestation of man is not a serious lethal factor in Missouri, since in 163 instances of infestation it was not held to have been the cause of death or to have contributed to the cause of death.

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THE EFFECT OF INDUCED HYPERPYREXIA ON THE UREA CLEARANCE OF RHEUMATIC PATIENTS.

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During the past few years the use of induced pyrexia in the treatment of certain disease conditions has become increasingly common. Various studies have been made of the physiological and biochemical changes resulting from artificial fever.[3,4] Further analysis of the effects of induced fever on different bodily functions and organs seems indicated since fever therapy is a strenuous procedure, and proper selection of patients is necessary to avoid untoward reactions. Since artificial fever therapy is still in the investigative stage, criteria for the use of and for contraindications to this type of treatment have not been completely worked out. The present study was undertaken to determine the effect of this sudden increase in body temperature upon renal function, as measured by the urea clearance. No other renal function tests were performed.

Method. Seven patients on the rheumatic fever service of this hospital, who had been selected for this treatment, were observed. All seemed to be in good condition, after allowances were made for their specific disabilities. Artificial fever was induced by placing the patient in a cabinet heated by five 200-W. carbon filament lamps. Only the patient's head and neck protruded from the cabinet, and a minimum of clothing, such as shorts and brassières, were worn, since direct radiant heat on the body hastened the rise of fever. Sedatives, usually nembutal, were given when necessary. Fluids such as water, fruit juices, ginger ale and broth were given as desired by the patient. In addition, all but 2 of the patients received ample quantities of sodium chloride by mouth, either in broth or in a 1% saline solution, in order to replace salt lost through sweating. Continuous temperature recordings were made by a rectal thermocouple and a Leeds and Northrup recorder. The temporal arterial pulse was recorded every 10 or 15 minutes or oftener if excessive tachycardia (above 150) or irregular pulse developed.

A satisfactory treatment was one in which an average rectal temperature of 105° F. was maintained for 5 hours. In some of the first treatments the desired level of 105° was not attained. About 1½ to 2 hours were required to reach this level, after which time the electric current through the lamps was reduced to maintain a fairly constant degree of fever.

Of the 7 patients receiving a total of 14 hyperpyrexial treatments, 2 had rheumatic fever, 3 had subacute or chronic infectious arthritis, 1 had gonococcal arthritis, and 1 had dermatomyositis. Both of the rheumatic fever patients had well-compensated cardiac valvular

TABLE 1.—DATA ON THE EFFECT OF INDUCED FEVER ON THE UREA CLEARANCE OF 7 PATIENTS.

Patient.	Date.	Time in minutes.	Urine volume, cc. per min.	Urine volume corrected, cc. per min.	Blood urea nitrogen, mg. per 100 c.c.	U/B.	Urea clearance, % normal.	Average.	Beginning of period. Temp.	Beginning of period. Pulse.	End of period. Temp.	End of period. Pulse.	Highest. Temp.	Highest. Pulse.	Approximate av. temp.	Change in body wt. during treatm't, kg.	Comment.
B. B. ♀	9/26/36	77	0.53	0.57	11.00	53.6	75.2		104.0	140	104.5	136	104.8	150	104.0	−0.1	Treatment well tolerated until menses began.
18 yrs.		249	2.03	2.18	....	32.6	94.9	85.0	....	..	100.4	108					
Gonococcal arthritis	10/2	71	0.54	0.58	13.98	58.6	82.2		104.0	120	105.8	128	106.1	158	105.0	+1.7	Treatments all well tolerated.
		116	0.48	0.52	....	79.7	106.3	96.5	....	..	104.5	124					
		160	0.53	0.57	....	72.2	101.0		....	..	105.0	126					
	10/6	66	1.38	1.48	9.00	46.7	105.3										
		64	2.66	2.86	....	24.0	91.5	98.4	Control								
	10/9	102	0.49	0.53	12.92	63.5	85.4		103.5	136	105.8	142	106.7	158	105.5	+1.7	Pt. out of box part time this period.
		253	0.51	0.55	....	66.8	91.9	88.6			102.0	102					
E. F. ♂	5/29/35	75	0.24	0.25	10.03	72.4	66.4	....	103.5	152	104.8	148	106.0	152	....	−1.2	Pt. unable to void again for 13 hrs. Nausea and vomiting. No salt given.
17 yrs.	7/1	65	1.14	1.16	10.47	50.6	101.2	89.2	Control								
Rheumatic fever		60	3.92	4.00	....	14.5	77.2										
S. S. ♂	6/19/35	60	0.27	0.33	10.26	44.7	47.7		103.8	142	105.5	144	105.5	148	105.0	+0.5	Treatment well tolerated. No salt given.
11 yrs.		102	0.78	0.97	....	18.2	33.3	40.5			105.2	146					
Rheumatic fever	7/1	60	0.83	1.03	9.22	77.6	146.2										
		60	1.58	1.97	....	47.7	123.8	135.0	Control								
W. L. ♂	11/1/35	60	0.27	0.25	15.10	21.8	20.3		106.3	164	105.2	160	106.3	164	105.0	−0.5	Treatments well tolerated. Moderate restlessness. Salted chicken broth given.
17 yrs.		118	0.56	0.53	....	63.6	85.8	53.0			105.2	146					
Chronic infectious arthritis	11/5	59	1.24	1.17	12.17	66.5	133.3										
		60	6.00	5.70	....	14.2	107.8	120.6	Control								
	11/7	65	0.43	0.41	15.27	39.6	46.9		106.5	136	106.0	144	106.5	156	105.5		
		60	0.53	0.51	....	53.4	70.4	58.7			104.5	140					

L. S. ♀	2/7/36	100	0.50	0.53	8.27	57.0	75.5		106.3	156	106.0	148	106.3	160	105.8	+0.4	Treatments well tolerated. Saline given. Pt. unable to void for 12 hrs. Treatments preceded by hot bath to produce preliminary fever. Pt. exhausted, nausea and vomiting. Heat not well tolerated.
26 yrs.		145	0.52	0.55	....	94.7	130.5	103.0			105.2	144					
Dermatomyositis	2/11	60	3.63	3.85	9.16	21.0	108.0				Control						
		60	12.46	13.20	....	6.0	105.0	106.5									
	3/13	175	0.80	0.87	13.16	17.4	30.0		106.0	142	105.8	140	106.2	160	105.5	+0.1	
		724	0.39	0.42	....	8.9	10.8	20.4			98.6	72					
	3/19	176	0.44	0.48	11.45	65.1	83.8		104.0	132	105.7	136	105.8	144	105.0	−0.9	
		114	0.35	0.38	....	89.6	102.5	93.2			104.7	130					
	3/21	60	1.03	1.12	10.61	57.8	113.4				Control						
		60	7.17	7.80	....	8.9	93.0	103.2									
V. S. ♀	4/8/36	60	1.50	1.58	13.09	15.7	36.6		102.5	124	105.5	144	106.3	144	104.8	+0.4	Pt. not coöperative, treatment not satisfactory. Pt. complained more than average.
44 yrs.		105	0.30	0.32	....	31.3	32.9	34.8			105.5	144					
Atrophic arthritis		175	0.67	0.71	....	16.0	25.0										
	4/11	60	2.10	2.21	14.87	20.7	60.9										
		60	5.50	5.79	....	13.3	102.8	81.8			Control						
	4/13	58	1.29	1.36	14.87	20.6	44.5		103.0	120	105.0	130	106.3	138	104.0		
		274	0.30	0.32	....	35.0	36.6	40.5			98.6						
D. S. ♂	1/7/36	229	0.93	0.89	14.16	46.8	81.7		105.0	146	105.5	152	106.5	156	105.5	+3.1	Treatment well tolerated; 24 hr. fluid intake 10,980 cc. and 10,350 cc. respectively; 4000 and 2000 cc. of 1% saline given during 2 treatments. Pt. out of box at end of 1st period and nearly normal. Unable to void during treatment.
20 yrs.		95	3.05	2.93	....	24.9	97.1	89.4			105.5	140					
Subacute infectious arthritis	1/14	60	1.62	1.55	10.69	48.1	111.0										
		58	1.98	1.90	....	40.7	104.0	107.5									
	1/16	305	1.61	1.54	9.68	38.3	88.0		103.8	140	out of	box	105.5	160	104.5	+1.4	
		120	4.67	4.48	....	13.9	82.8	85.4									

Average urea clearance: First fever period = 61.7; first control period = 109.8. Second fever period = 75; second control period = 100.

lesions. Objectively, all treatments were well tolerated, and except for mild hysteria during two treatments no untoward symptoms were noted.

The clearances were begun after the patient's temperature had been increased to about 104° F. At this time a urine specimen was obtained. The first clearance period generally lasted from this time until the temperature reached its maximum. The second period roughly covered the time during which the temperature remained at its highest point. It was not always possible for the patient to void when asked, because of the profuse loss of water by sweating, so in many instances the first period included part of the time the patient was showing the maximum temperature. Blood was obtained at the end of the first period.

Results. The data thus obtained are shown in Table 1. The average urea clearance during the period when the temperature was rising was 61.7% of normal, and during the period when the temperature was at a maximum the clearance averaged 75% of normal. In 2 instances (E. F. and L. S.) a severe oliguria resulted from the treatment, and these patients were only able to void after 12 hours. For the entire group the average control clearance was 105% when the patients were afebrile.

Discussion. The effect of high artificial fever on dogs has been studied by Knudson and Schaible,[3] who found a marked decrease in blood volume. They attributed this to fluid loss, which seems reasonable since they gave their animals no fluid. This dehydration factor consequently obscures the effect which the temperature elevation exerted itself, and it seems likely that the blood changes they noted were due chiefly to desiccation. Moen, Medes and Chalek[4] observed dogs with artificially induced fever in which attempts were made to overcome the dehydration factor. They noted only minor changes in both total plasma protein and the plasma-protein fractions of these dogs. No data were given concerning non-protein nitrogen.

In patients with Bright's disease in this clinic, a significant direct relationship between fever and the urea clearance has not been noted. Goldring[2] found the urea clearance slightly elevated in active febrile rheumatic fever; and Farr and Abernethy[1] found a marked elevation of the urea clearance in pneumonia which was not related to temperature. On the other hand, Page[5] found no change in urea clearance during diathermy treatment applied locally over the kidney region.

In dogs, Van Slyke, Rhoads, Hiller and Alving[6] found the urea clearance varied in direct proportion to the renal blood flow. In our patients the mechanism producing the lowered clearance was presumably a retarded renal blood flow. Possible causes of the retarded renal circulation may have been either deflection of blood from the kidneys to the hyperemic skin,[3] or occurrence of some desiccation[4]

despite the precautions taken to prevent it. The decrease in renal function was not serious in any of our patients, and was transitory. The fact that a definite decrease occurred, however, emphasized the desirability of combating desiccation during the febrile treatments, and of applying them with caution to patients with damaged kidneys, until their effects in such patients have been studied.

Summary. Urea clearance tests were done on 7 patients before, during, and after hyperpyrexia was artificially induced.

The average urea clearance was 61.7% of normal during the period when the fever was mounting, and 75% when the fever was maintained at its maximum. The control clearances on these patients averaged 105% of normal.

The data indicate the desirability of combating dehydration during fever therapy.

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THE EFFECT OF BENZEDRINE, BENZEDRINE AND ATROPINE, AND ATROPINE ON THE GALL BLADDER.*

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The physiologic actions of benzedrine sulphate (phenylisopropylamine sulphate) are primarily those following stimulation of the sympathetic division of the autonomic nervous system.[1–13,15,16] In the gastro-intestinal tract it has been demonstrated that benzedrine increases the acidity and pepsinogen of the gastric juices,[9] and decreases the tonus of the entire gastro-intestinal tract.[7]

Because of the relaxation obtained by the use of benzedrine in the gastro-intestinal tract we have decided to extend our work on benzedrine to cover the total digestive apparatus, and in this particular instance to investigate the effects of benzedrine upon the gall bladder. In a preliminary study,[14] we found that the gall bladder emptied normally when a fatty meal was administered within

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½ hour after the benzedrine, but that it failed to empty when a fatty meal was given at least 2 hours after the drug. The observation[8] that paralysis of the parasympathetic nervous system by atropine enhanced the effect of benzedrine on general body physiology has stimulated the additional investigation of the effect of the combination of benzedrine and atropine on the gall bladder. To complete our study, the effect of atropine alone on the gall bladder was carried out. It is the purpose of this paper to present these observations.

Method. The individuals used in this work were all mentally ill but physically normal. They coöperated well throughout the period of the study. All were males with an age range of 32 to 51 years. Each patient was used as a control on himself and on the entire group.

Control Study. Before the benzedrine study was started each patient received a gall bladder dye test to determine the size and rate of emptying of this viscus. The night before the test the patient received a light meal consisting of dry toast, tea and sugar. One hour later he was given the gall bladder dye, tetro-iodo-phenolphthalein sodium, orally. The following morning, after a fast of at least 15 hours, Roentgen ray films were taken of the gall bladder region. Then he was given a meal rich in fat, consisting of two slices of white bread thickly spread with butter, and 2 glasses of milk and cream mixture into which had been beaten 4 raw eggs. After a lapse of 1 to 2 hours Roentgen ray films were again taken. Only those individuals were used in whom there was either a marked diminution or complete disappearance of the gall bladder shadow on the Roentgen ray films taken after the fatty meal. This method of dye administration and type of meal were used throughout the work.

Benzedrine Study. In this series, after initial Roentgen ray films of the dye-filled gall bladder, the patient was given 30 mg. of benzedrine subcutaneously. One-half hour later, films were taken and the patient immediately given a fatty meal. Films were then repeated at 30 and 60-minute intervals.

Benzedrine and Atropine Study. The same procedure was followed as in the benzedrine study excepting that atropine, gr. 1/100, and benzedrine, 30 mg., were administered subcutaneously and at the same time.

Atropine Study. Again the same procedure was followed as in the benzedrine study excepting that atropine, gr. 1/100, but no benzedrine, was given subcutaneously.

Each of these procedures was carried out on every patient. Twenty-two such studies were made. The benzedrine was used as benzedrine sulphate, and the atropine as atropine sulphate. The drugs were always given subcutaneously.

Results. Chart 1 demonstrates the effect of benzedrine, benzedrine and atropine, and atropine on the gall bladder; it also illustrates the ability of these drugs to prevent the emptying of the gall bladder after a fatty meal is given. This chart shows that: 1. The size of the gall bladder is affected very little by benzedrine. In 1 of our cases there was a slight increase in the size of the gall bladder,

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LEGEND FOR CHART 1.

CHART 1.—Changes in the gall bladder shadow following the use of benzedrine 30 mg., benzedrine 30 mg. and atropine 1/100 gr., and atropine 1/100 gr. subcutaneously.

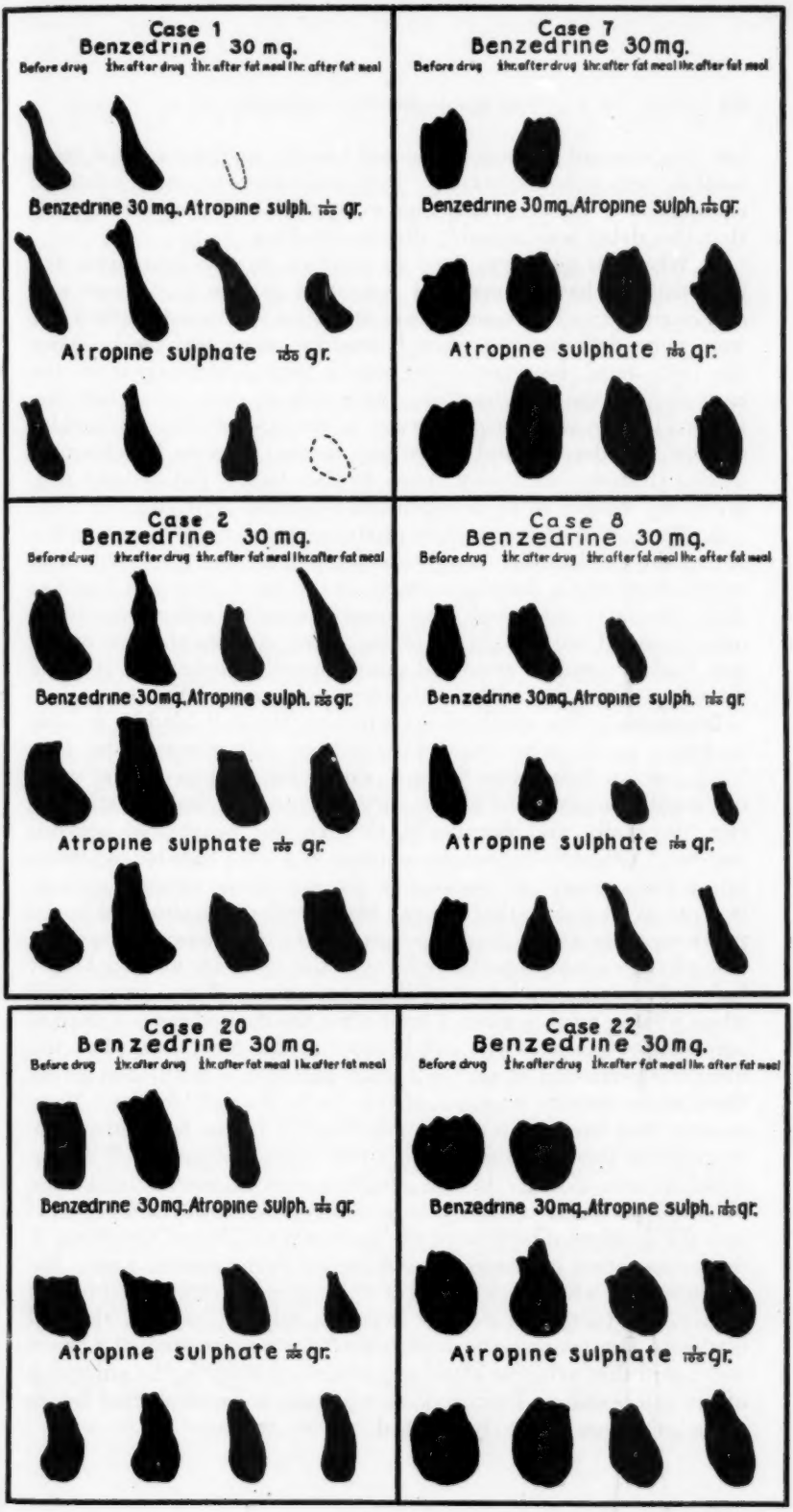
Case 1
Benzedrine 30 mg.
Before drug
½hr. after drug
½hr. after fat meal
1hr. after fat meal
Benzedrine 30 mg., Atropine sulph. 1/100 gr.
Atropine sulphate 1/100 gr.
Case 7
Benzedrine 30mg.
Before drug
½hr. after drug
½hr. after fat meal
1hr. after fat meal
Benzedrine 30mg., Atropine sulph. 1/100 gr.
Atropine sulphate 1/100 gr.
Case 2
Benzedrine 30 mg.
Before drug
½hr. after drug
½hr. after fat meal
1hr. after fat meal
Benzedrine 30mg., Atropine sulph. 1/100 gr.
Atropine sulphate 1/100 gr.
Case 8
Benzedrine 30 mg.
Before drug
½hr. after drug
½hr. after fat meal
1hr. after fat meal
Benzedrine 30mg., Atropine sulph. 1/100 gr.
Atropine sulphate 1/100 gr.
Case 20
Benzedrine 30 mg.
Before drug
½hr. after drug
½hr. after fat meal
1hr. after fat meal
Benzedrine 30mg., Atropine sulph. 1/100 gr.
Atropine sulphate 1/100 gr.
Case 22
Benzedrine 30mg.
Before drug
½hr. after drug
½hr. after fat meal
1hr. after fat meal
Benzedrine 30mg., Atropine sulph. 1/100 gr.
Atropine sulphate 1/100 gr.

CHART 1.

but this was not striking. The gall bladder emptied after a fatty meal in every instance but one. In this case there was a very definite retardation of the emptying time even after 1 hour and it was felt that this delay was probably due to the drug.

2. When atropine was used in addition to the benzedrine the gall bladder shadow increased somewhat in size in 3 cases and decreased in size in 1 case. These alterations were not marked but were more definite than when benzedrine alone was used. After the fatty meal, however, there was a very definite delay in the emptying of the gall bladder. Although in every case but one (Case 7) there was some decrease in the size of the gall bladder shadow, this decrease did not by any means eradicate the clearness of this shadow. In 1 case (Case 8) the shadow did become progressively smaller so as to approximate normal emptying.

3. The use of atropine alone produced little or no change in the size of the gall bladder shadow excepting in 2 cases (Cases 2 and 7) where there was a definite increase in the size of the gall bladder. After the fatty meal had been given the gall bladder emptied in only 1 case (Case 1). In all of the other patients the size of the gall bladder shadow remained approximately unchanged and the retention of the dye within this viscus was quite definite.

Discussion. The mechanisms whereby the gall bladder is able to empty itself or be emptied have been ably discussed by Ivy. They resolve themselves into: *a*, direct stimulation of the walls of the gall bladder physically or chemically; and, *b*, indirect stimulation physically and chemically through the autonomic nervous system. Although benzedrine sulphate is a drug capable of stimulating the sympathetic division of the autonomic nervous system, it is not at all certain that the gall bladder effects as observed in our previous study and in this paper are due to this power of the drug. The physiologic (autonomic) effects of this drug are at their height before 30 minutes and most of them have worn off in 1 hour. Still when a fatty meal is given ½ hour after the drug there is a normal emptying response of the gall bladder to the meal, but when the drug was permitted to act for 2 hours and then a fatty meal given, there was a definite retention of the dye in the gall bladder. If we assume that the action on the gall bladder is due to sympathetic stimulation then we must assume that some mechanism is set up which causes a delay in the establishment of such stimulation. Whether this delay is due to the retarded progress of the fatty meal into the duodenum because of the decreased motility of the stomach or to some other mechanism is not known at the present time. We do know that when the motility of the stomach is diminished by use of atropine there is a definite delay in the emptying of the gall bladder. However, the authenticity of this was questioned when it was found that atropine alone will produce a delay in the emptying of the gall bladder. Further work will have to be conducted before these points are definitely clarified.

The observations of Myerson that paralysis of the parasympathetic system by the use of atropine apparently enhances the action of the sympathetic stimulant benzedrine suggests a constantly active system of checks and balances existing between the sympathetic and parasympathetic systems. He states that when the sympathetic division of the autonomic nervous system is stimulated, as by benzedrine, a complete effect may not be obtained because of the continued activity of the parasympathetic division and that when the latter is paralyzed the complete effect is obtained. His conclusions are not borne out in our studies on the gall bladder. In these it would appear that the benzedrine interfered with the effect on the gall bladder obtained by atropine; that when atropine alone was used a better retention was obtained than when benzedrine and atropine were used.

From these studies it seems that, except in the odd case, benzedrine delays the emptying of the gall bladder only after a long period has lapsed following administration of the drug; and that sympathetic stimulation, if it is effective, occurs only after a prolonged period. It would appear that the combination of a sympathetic stimulant and parasympathetic paralysant is effective in delaying the gall bladder emptying, but that this effect is not so marked as when the parasympathetic paralysant, atropine, is used alone. It cannot definitely be stated whether these results are due to direct or to indirect action of the drug on the gall bladder. It seems, however, that although the results obtained by the use of benzedrine are questionably sympathetic, those obtained by use of atropine are definitely due to parasympathetic paralysis. This would indicate that should a drug be desired to relax the gall bladder walls or to inhibit emptying of the gall bladder, a parasympathetic paralysant would be of greater value than a sympathetic stimulant.

Summary. The results of the effect of benzedrine, benzedrine and atropine and atropine on the gall bladder are presented. The immediate effects of benzedrine on this viscus are negligible; benzedrine and atropine combined definitely delay the emptying of the gall bladder but not as adequately as atropine alone.

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PATHOLOGICAL PHYSIOLOGY OF PULMONARY CYSTS AND EMPHYSEMATOUS BULLÆ.

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Koontz[14] first called the attention of the American clinicians to congenital cystic disease of the lung, when he reported a case in 1925 and collected from the European literature 108 additional cases. Since that time numerous case reports have appeared. Most observers have been chiefly concerned with the etiologic factors, pathogenesis, pathologic observations, symptomatology and roentgenographic studies of such anomalies. Investigating a large group of men with chronic respiratory disorders over a period of 3 years, we found 6 individuals whose roentgenograms showed annular shadows of varying size and extent. Our main objectives in making this study were to seek an explanation for the mechanism of dyspnea which appeared to be the cardinal symptom and the chief cause of disability and to determine whether the abnormality was congenital or the result of obstructive emphysema, *i. e.*, emphysematous bullæ.* The majority of the cases herein reported had in addition to the air filled cysts, pulmonary fibrosis or obstructive emphysema. Thus far we have not encountered a case that simulated "honey comb lung" or one that would be confused with congenital bronchiectasis. From a review of the literature there appears to be no uniformity of opinion as to how one can differentiate clinically congenital cystic disease of the lung, congenital bronchiectasis or acquired cavities filled with air resulting from the breakdown of pulmonary tissue. This communication presents the results of a study from the functional viewpoint of 6 cases with cystic changes of the lungs and emphysematous bullæ.

* The term "bulla" is used in this paper as defined by W. S. Miller.[16a] "A *bleb* was caused by a rupture of the pulmonary alveoli immediately beneath the pleura which allowed air to escape into the pleura and caused it to separate from the underlying alveoli, thus forming a thin-walled space situated outside of the lung itself; while in the case of a *bulla*, although the alveoli beneath the pleura were greatly distended, and eventually by the destruction of the interalveolar walls formed a large space that often projected beyond the level of the surrounding pleura, it was situated within the lung and was covered by the intact pleura. In other words, a *bleb* is an interstitial emphysema situated within the pleura and causes those thin-walled, bladder-like prominences which are found on the surface of the lung, while a *bulla* is due to a vesicular emphysema situated within the lung and though it often projects beyond the surface of the lung is covered by an intact pleura."

Case Reports. CASE 1.—C. D. (No. 52358) was a 35-year-old coal miner who was admitted to the Strong Memorial Hospital November 13, 1933, with the chief complaint of shortness of breath. The patient dated the onset of his present illness to 1917 at which time, while in the army, he had an attack of abdominal pain accompanied by diarrhea of 3 weeks' duration. Since that time there has been a progressive increase in dyspnea and marked constipation. After discharge from the army, the patient continued his usual occupation (coal mining) until 1926, when he had to quit his job for a less strenuous one because of breathlessness. Since the onset of the illness there has been a constant cough productive of thick yellow sputum, never blood tinged and more marked in the morning. In 1918, 1923 and 1925 there were attacks of "bronchitis" with fever and an increase in the productive cough. He had noticed clubbing of the fingers for 20 years. There was a gradual loss of weight from 88.6 kg. in 1917 to 48 kg. in 1933. There was no history of precordial pain, edema or orthopnea. In fact during the 2 years prior to admission he was more comfortable lying flat in bed than in an upright position. Since 1931 he had been practically bedridden because of severe dyspnea.

Prior to 1919 his general health was excellent. As a child he had measles complicated by pneumonia. He worked in bituminous coal mines for 13 years.

Physical Examinations. The temperature was 37° C. The patient was a well developed but undernourished man, who appeared acutely ill. His characteristic position in bed was fully supine with his arms extended above his head grasping the head of the bed. Respirations were rapid (28 per minute) and labored. With each inhalation the inspiratory muscles of the neck were very tense and prominent and the supraclavicular fossæ were markedly accentuated. When the patient assumed the sitting position the respirations became more rapid and dyspnea more marked. Talking and eating greatly accentuated his respiratory distress. The mucous membranes of the lips and eyelids and the finger nail beds were cyanotic. There was marked clubbing of the finger and toes. The chest was symmetrical with an increase in the anteroposterior diameter. The lower part of the chest cage flared moderately. Expansion of the chest was limited bilaterally. All the respiratory muscles were well developed in contrast to the general musculature. The percussion note had a tympanitic quality. The precordial and hepatic dullness was obliterated. Tactile fremitus was poorly transmitted over the whole chest except at both bases where it was increased. The pulmonary bases descended poorly. Over the upper half of both lungs the breath sounds were diminished, while at the bases they were exaggerated and very harsh. The heart could not be outlined by percussion. The rhythm was regular. There were no audible murmurs. The pulse rate was 80 per minute. The blood pressure was 92/70 mm. of mercury. There was no peripheral edema.

Laboratory Data. The red blood cell count was 5.8 millions per c.mm.; hemoglobin, 19 gm. per 100 cc. of blood; white blood cell count, 11,200 with a normal differential count. The blood Wassermann test was negative. Repeated search for acid-fast bacilli in the sputum was negative. The electrocardiogram showed right axis deviation. Roentgenogram of the chest (October 5, 1931 and November 14, 1933, see Fig. 1) showed a large pocket of air in both pleural spaces which extended as low as the sixth interspace on the left and the seventh on the right. The lungs were compressed toward the diaphragm and occupied about one-third of the pleural spaces. There were many small dense calcified areas in both lungs at the level of the ninth and tenth posterior ribs. The heart was normal in size and shape.

Course. On November 15, 1933, a needle was inserted into what was thought to be the right pleural cavity. The pressure was −6 mm. of water at the end of inspiration and +5 cm. at the end of expiration. Air (2000 cc.) was removed without change in the symptoms, intrapleural pressure or in the size of the cavity. A like procedure was carried out on the left side with similar results. On December 6, 1933, a thoracoscopy was performed on the left side by the late Dr. E. W. Phillips, for the purpose of locating a pleuro-bronchial fistula. Portions of the lung were found to be of normal pink color and apparently air containing, while other portions were of deep bluish color apparently atelectatic. There were several adhesions passing between the lung and the chest wall and between different portions of the collapsed lung. Still being of the opinion that this was a case of a bilateral pneumothorax with a pleural-bronchial communication, on December 27, 1933, Dr. Phillips performed an exploratory thoracotomy on the left side and found a large air cyst which filled the upper half of the chest. The cyst was removed and the patient died about 2 hours after the operation.*

Clinical Diagnoses. Pulmonary fibrosis, anthracosilicosis; bilateral emphysematous bullæ; congenital cystic disease of the lung (?)

Autopsy (No. A-2476, performed by Dr. Ralph E. Knutti). The heart weighed 260 gm. The right auricle and ventricle were slightly dilated. The most striking feature was the marked right ventricular hypertrophy. The walls of which measured 1.2 cm. in thickness. The left ventricular wall averaged 1.2 cm. in thickness. The myocardium showed no abnormalities. All the valves appeared normal. The coronary orifices were patent. The arch of the aorta had a smooth intimal surface. The coronary arteries were wide and showed in some places, particularly where branches existed some tiny, yellow subintimal plaques. *Lungs:* The left weighed 500 gm. The right was not weighed (see roentgenogram of the right lung after removal, Fig. 2). The left lung had a deep blackish-red color. It was subcrepitant in the central portions of the lobes and crepitant at the margins. The margins showed numerous, quite large (up to 1.5 cm. in diameter) cushiony, thin-walled bullæ. Some of these were single; others apparently represented whole lobules. The central portions of the lobes were partially collapsed, elastic, soft and black in color. There was no consolidation and no resistance to section. No fibrous nodules were noted. The bronchi showed no dilatation. The bronchial mucosa was smooth. The pulmonary arteries showed marked, quite sizable yellow subintimal streaks and plaques. The right lung, at the upper portion of the upper lobe, contained a tremendous, round thin-walled, semi-transparent sac filled with air. It measured 15 by 15 by 10 cm. and was single (Fig. 2). The lung elsewhere showed cushiony emphysematous bullæ at the margins of the lobes, similar to those seen in the left lung. The main portions of the lobes appeared to be partially collapsed. There was no external or palpable evidence of consolidation or nodulation. On section of the right lung, there was a large fibrous walled cyst at the apex with reduction of the upper lobe by about one-half (Fig. 3). The lung tissue formed the lining of the lower part of the cyst and thin interlacing bands of connective tissue stretched out to the walls of the cyst laterally. Throughout the remainder of the lung there was marked emphysema particularly in the lower lobe where several bullæ 2 cm. in diameter were found with adjacent air sacs greatly enlarged. Anthracosis was very marked.

Microscopic Notes. Section through the hilus of the left lung showed marked fibrosis and coal pigmentation. Large lamellated nodules were present, composed of hyalinized connective tissue with calcified centers. In the fibrous tissue about the nodules, there was a tremendous amount of black pigment material. Metaplastic alveolar epithelium was included in

* This patient was kindly referred to us by Dr. John J. Lloyd.

some strands of fibrous tissue. The alveoli outside the most marked fibrotic areas were collapsed. The alveolar walls were markedly infiltrated with coal pigment. The pulmonary vessels showed marked intimal thickening. The bronchi had greatly thickened walls which were infiltrated with chronic inflammatory cells. A section through the lung, away from the hilus, showed a considerable thickened pleura which, in the subepithelial fibrous tissue, showed marked black pigment infiltration. Alveolar epithelium adjace t to this fibrous layer was markedly metaplastic. Alveolar walls were everywhere greatly thickened. Even greatly dilated emphysematous alveoli which were quite numerous, showed walls considerably thicker than those of a normal alveolus. Many of the alveolar walls, especially the thicker ones, near the pleura, which were obviously fibrotic, contained considerable black pigment, most of which was presumably in large mononuclear phagocytic cells. Sections through the main pulmonary arteries showed marked intimal thickening and proliferation with fatty, subintimal plaque formation. Sections through the wall of the large cystic space of the right lung showed a pleura which varied in thickness, but was not, in the section studied, greatly thickened (Fig. 4). It was infiltrated with chronic inflammatory cells and contained black pigment and occasional groups of metaplastic alveolar epithelial cells. The remainder of the wall was composed of flattened alveoli, all compressed in a longitudinal plane; the walls of these were thickened with fibrous tissue. The other showed considerably thinned walls. Those that were considerably thickened were lined with metaplastic epithelium. The inner surface was composed of alveolar walls, some apparently being part of greatly dilated flattened alveoli; others projecting into space, being connected with other walls at the inner surface. Some flattened bronchi with metaplastic epithelium were noted. Sections from other portions of the right lung showed marked emphysema and atelectasis, marked fibrosis with nodular formations of hyalinized lamellated connective tissue and marked dilatation and collapse of alveoli and most marked black pigment infiltration.

Anatomic Diagnosis: Massive emphysematous bullæ, bilateral; pulmonary emphysema and atelectasis; pulmonary arteriosclerosis; pulmonary fibrosis; anthracosilicosis (marked); cardiac hypertrophy, right ventricle; clubbed fingers.

Case 2.—A. W., was a 55-year-old man who complained of shortness of breath. Because of medico-legal considerations we were unable to obtain a satisfactory history. He was exposed to considerable amounts of dust, some of which presumably contained silica. Dyspnea was produced by the slightest exertion. The roentgenograms of the chest are reproduced in Figures 5 and 6. The chest cage appeared slightly asymmetrical with wider rib spaces on the right, particularly over the lower portion of the right lung. The left leaf of the diaphragm was noted in a low position and sloped gradually to a broad costophrenic angle. The left leaf was somewhat indistinct and the angle on this side was partly obscured. The heart was not enlarged in the posterior anterior projection. However, the pulmonary artery appeared very prominent in both the posterior anterior and lateral projections. The aortic knob was not unusually prominent. The right pulmonary field in general appeared more radiotranslucent than the left. The markings on this side at the infraclavicular level radiated outward without any disturbance in general contour. The lower part of the right lung showed numerous radiotranslucent areas suggesting the presence of air cysts or bullæ. Over the lower part of the right lung the presence of these cysts had disturbed the alignment of the usual linear markings. They have been deflected medially and forward. The lung markings appeared increased. This was apparent over the right lower lung and throughout the left. The hilar structures appeared somewhat prominent. About the upper

pole of the left hilum there were shadows of increased density suggesting fibrosis while at the left pulmonary base the shadows appeared very dense and extended down to the level of the diaphragm. The prominence of the pulmonary artery may be taken as evidence of hypertension of the lesser circulation.

Clinical Diagnoses. Pulmonary fibrosis; congenital cystic disease of the lung.

CASE 3.—J. L. (No. 74455) was a 59-year-old belt cutter admitted to the Rochester Municipal Hospital on April 26, 1933, complaining of shortness of breath for 1 year and asthma of 14 years' duration. He had a chronic cough productive of small amounts of phlegm for 14 years, associated with frequent paroxysms of bronchial asthma. Recently the cough had gradually become worse and for the past year he had increasing dyspnea on exertion without edema or orthopnea.

On *physical examination* the temperature was normal, the pulse 90 and the respirations 20 per minute. The blood pressure was 130/80 mm. of mercury. He was an undernourished man of 59, who did not appear ill. There was slight clubbing of the fingers. The mucous membranes were cyanotic. The thorax was symmetrical with an increase in the anterio-posterior diameter. Percussion note had a tympanitic quality. Wheezing breath sounds were heard over both pulmonary fields accompanied by fine scattered crepitant râles over the upper portions of the lungs and moist râles over both bases. The heart was not enlarged. Rhythm was regular except for an occasional extra systole. There was a systolic whiff over the aortic area.

The patient was again admitted to the hospital in July, 1935, at which time the studies reported in this paper were made. At that time he remarked that shortness of breath was more easily induced than formerly, but there were no other symptoms or signs of congestive heart failure.

Laboratory Data. The red blood cell count was 3.45 million; hemoglobin, 10.5 gm. and white blood cell count 7000 with a normal differential count. The blood Wassermann test was negative. The electrocardiogram showed left axis deviation and occasional ventricular extrasystole. Roentgenogram of the chest (July 29, 1935) showed the right upper pulmonary field above the sixth interspace posteriorly to be unusually brilliant. It lacked the usual normal markings seen in the left side. The markings seem to run

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LEGENDS FOR FIGS. 1, 2, 5 AND 6.

FIG. 1.—Roentgenogram of the chest of a case (C. D.) of Bilateral Emphysematous Bullæ. Note the marked displacement downward of both hilar structures, the complete absence of all pulmonary markings over the upper portions of the pulmonary fields and the compact character of the markings at the pulmonary bases, many of which describe curved course as a result of pressure by adjacent bullæ.

FIG. 2.—Roentgenogram of the right lung after removal from the thorax (Case C. D.). The large cyst (filled with fixing fluid) is shown in the upper lobe, while many smaller bullæ are seen around the peripheral portions of the lower lobe.

FIG. 5.—Roentgenogram of the chest of Case 2 (A. W.). The right lower pulmonary field shows an area of decreased density over which few pulmonary markings can be outlined. The markings bordering along the upper and medial aspects of this shadow are deflected upward and medially, their normal distribution being disturbed by pressure exerted by cysts. Note also the tilting upward of the interlobar septum between the right upper and middle lobes. On the left side, the changes relate chiefly to fibrosis.

FIG. 6.—Roentgenogram of the chest, lateral view (Case A. W.). The actual borders of several of the larger cysts can be outlined much more clearly in the lateral projection than in the usual postero-anterior film. Note the prominent shadow of the pulmonary artery beneath the aortic arch.

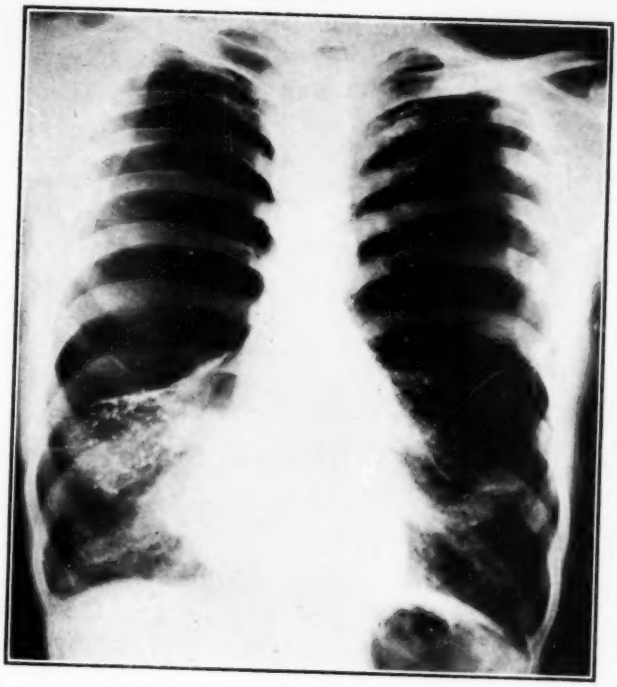

FIG. 1

FIG. 2

FIG. 3.—Section of the right lung showing the interior of the large emphysematous bulla with several smaller ones. The fine interlacing strands have been retouched.

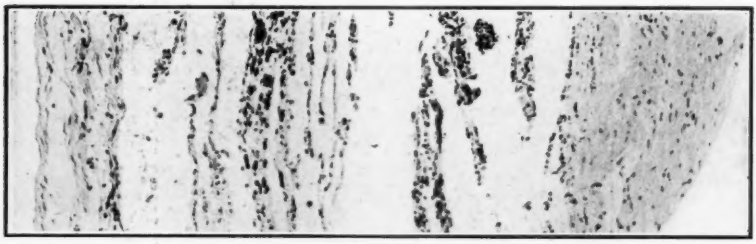

FIG. 4.—Photomicrograph of the wall of the large emphysematous bulla (Case C. D.). Magnification 100 ×.

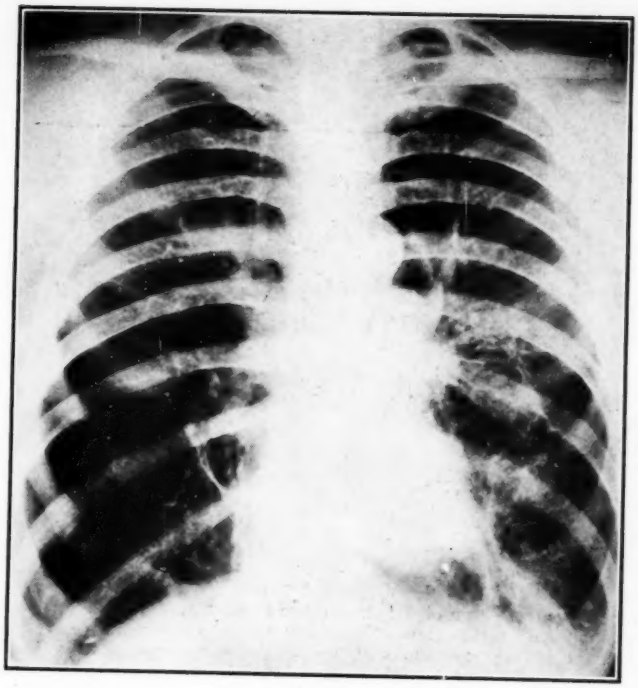

FIG. 5

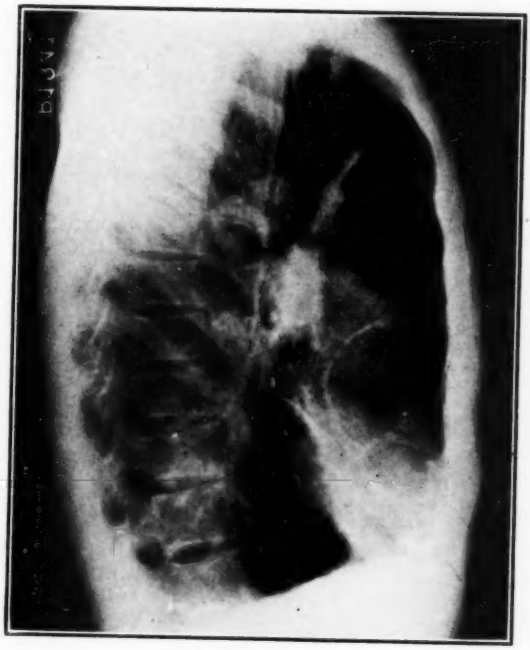

FIG. 6

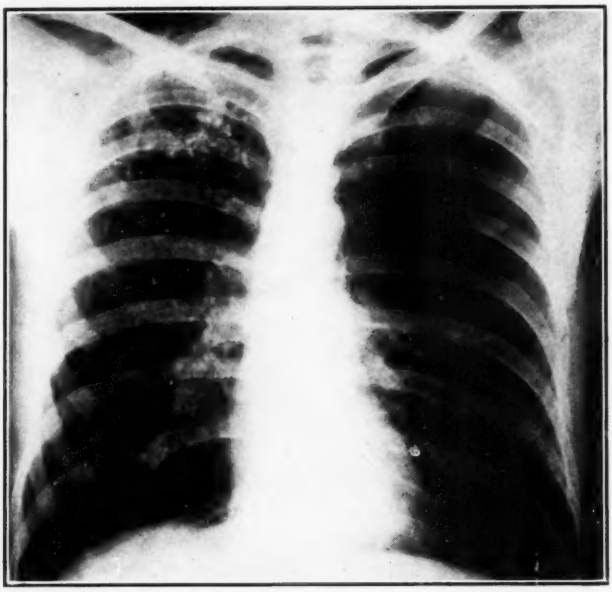

FIG. 7.—Roentgenogram of the chest (Case 5, R. W.). The left pulmonary field appears abnormally brilliant with very few pulmonary markings over its upper portion. The upper pole of the left hilum appears compressed and displaced downward. The densities over the right upper lobe relate to an old minimal tuberculosis with calcification.

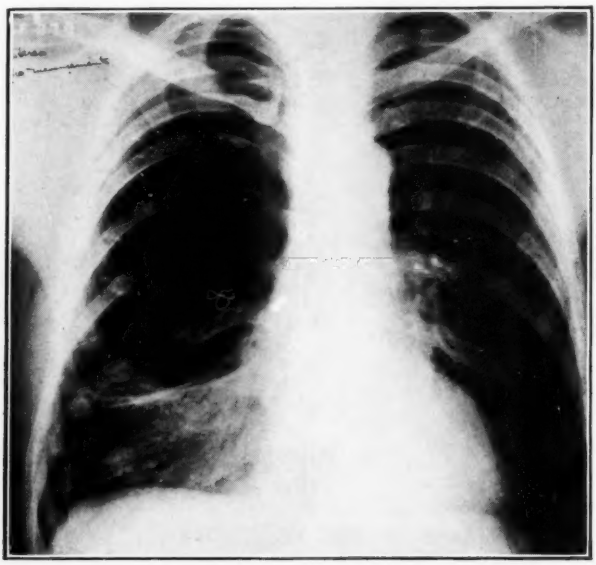

FIG. 8.—Roentgenogram of the chest (Case 6, J. D.). The right pulmonary field of this case is very similar in general appearance to that observed in Case 1: (*a*) abnormal brilliancy of upper right pulmonary field, (*b*) absence of the right hilar structure at its usual level, (*c*) the disturbed curved course of the pulmonary markings at the lower border of this shadow. Note the linear shadow crossing the lower right pulmonary field cast by the interlobar septum. The position of this septum suggests that the right upper lobe occupies at least three-quarters of the entire pulmonary field.

across the pulmonary fields and apparently outlined a large emphysematous bulla. The hilar structures were prominent. The diaphragms were low in position and on fluoroscopic examination the excursions of both diaphragms were diminished. The measurements of the heart were within normal limits. The pulmonary artery was prominent.

Clinical Diagnoses. Obstructive pulmonary emphysema; emphysematous bulla; bronchitis, chronic; asthma, bronchial.

CASE 4.—E. W. (No. 105034) was a 54-year-old laborer who was examined because of a history of exposure to silica. His chief complaints were "asthma" and frequent colds. For many years he had one or two chest colds every winter with right sided pleural pain of 2 or 3 weeks' duration. During these attacks he had a productive cough without fever. He complained of dyspnea on moderate exertion and he had asthmatic attacks for the past 4 years. During the past 12 years he had been working in grinding and mixing mills where he was exposed to considerable amounts of dust. In the past he had pneumonia at 19 years, typhoid at 20 and repeated attacks of sinusitis.

On *physical examination* the temperature, pulse, and respiratory rate were normal. The blood pressure was 110/70 mm. of Hg. The patient was a tall, thin man who appeared chronically ill. There was no cyanosis, clubbing of the fingers or edema. The thorax was of the asthenic type. Inspiratory retraction was marked in both supraclavicular fossæ. The left chest moved better than the right. The bases descended 4 cm. on the right and 6 cm. on the left. The percussion note had a tympanitic quality with dullness in the right interscapular region and right base posteriorly. Breath sounds were vesicular, accompanied by wheezing rhonchi. In the right mid-scapular region bronchial breathing was heard. From this region to the base and in the axilla coarse râles were heard on quiet breathing and after expiratory cough. The heart measured 10.5 cm. in the fifth interspace. The retromanubrial dullness was 7.5 cm . The rhythm was totally irregular in rate and force. There were no audible murmurs. The radial arteries were markedly sclerotic.

Laboratory Data. The red blood cell count was 5.59 millions; hemoglobin, 14 gm. per 100 cc.; white blood cell count, 11,300 with a normal differential count. The blood Wassermann test was negative. The electrocardiogram revealed auricular fibrillation. Roentgenogram of the chest showed the right diaphragm to be irregular and the costophrenic angle obliterated. Both pulmonary fields showed an extensive diffuse pulmonary fibrosis. On the right side large masses of fibrotic tissue were observed along the right axillary margin and at the level of the right hilus. The upper pole of the right hilus was enormously increased in size and density. The right apex and upper portion of the infraclavicular region on the right side was exceptionally brilliant. The right base showed diffuse fibrosis without the presence of agglomerated masses. On the left side the fibrosis appeared less marked though it extended from the apex to the base. The pulmonary field on this side showed no large fibrotic masses. The left hilus was greatly increased in size and density.

Clinical Diagnoses. Emphysematous bullæ; pulmonary fibrosis; obstructive pulmonary emphysema; heart disease, arteriosclerotic with auricular fibrillation.

CASE 5.—R. W. (No. 101120) was a 39-year-old delivery man complaining of asthma and shortness of breath of 3 years' duration. The present illness began with a "head cold" associated with wheezing respirations. Since that time he had had intermittent paroxysms of asthma during the day and almost constantly at night. Two years before admission he had a purulent sinusitis. During the 3 months prior to admission dyspnea was so severe he had to stop working. In the past he had pneumonia at the age of 28. He had never been exposed to any known industrial hazard.

Physical examination revealed an undernourished man, acutely and chronically ill. He was sitting upright in bed in evident respiratory distress. He had severe paroxysms of cough productive of small amounts of purulent sputum with occasional blood streaking. The mucous membranes were cyanotic. The upper left chest was more prominent than the right with a definite lag on deep inspiration. Expansion of the chest was diminished bilaterally. The percussion note was impaired from the right apex to the third interspace anteriorly and to mid-scapular area posteriorly. Over this area tactile fremitus and voice sounds were exaggerated. Over the left upper chest, both anteriorly and posteriorly, the percussion note had a tympanitic quality, tactile fremitus was poorly transmitted and breath sounds were diminished. There were no audible wheezes such as were heard over the remainder of the chest. The heart was not enlarged. The rhythm was regular. There were no murmurs heard. The blood pressure was 104/60 mm. of mercury.

Laboratory Data. The red blood cell count was 4.97 millions; hemoglobin, 15 gm. and white blood cell count, 9900. The electrocardiogram was normal. The blood Wassermann reaction was negative. The roentgenogram of the chest (Fig. 7) showed many calcified areas in the right lung from apex to the level of the sixth posterior rib. There were increased linear markings with rather coarse feathering in the right lung from the sixth posterior rib to the base. The left pulmonary field showed a large area of decreased density above the level of the seventh posterior rib. Fine interlacing lines traversed this area. There were increased linear markings with rather coarse feathering in the left lung from the seventh posterior rib to the base. The heart was shifted toward the right side.*

Clinical Diagnoses. Chronic bronchitis; bronchial asthma; obstructive pulmonary emphysema; emphysematous bullæ; chronic fibroid tuberculosis, right apex.

CASE 6.—J. D. (No. 69826) was a 38-year-old electro-plater who had no complaints referable to his cardio-respiratory system save for some limitation in exercise tolerance. The lesions in the lung were found when a roentgenogram of the chest was taken prior to a major abdominal operation. In the past he had a history of chorea at the age of 8 years, and pneumonia with pleurisy at 16 years. Since then he had had recurrent attacks of pleural pain without cough or fever.

Physical examination revealed a well developed and nourished man of 38, who did not appear ill. There was no respiratory distress, cyanosis or clubbing of the fingers. The thorax was symmetrical and expansion limited bilaterally. The percussion note was resonant throughout both lungs except at the right base where there was slight impairment. The left base descended farther than the right. The breath sounds over the left lung were normal. On the right anteriorly the breath sounds were suppressed and broncho-vesicular in quality. At the right base posteriorly the breath sounds were broncho-vesicular in type, accompanied by fine crackling râles. The heart was slightly enlarged to the left. There was no enlargement to the right. The first sound at the mitral area was accentuated followed by a short whiff. The pulmonic second sound was greater than the second aortic sound. There was a fairly loud early diastolic murmur heard just to the left of the sternum in the fourth and fifth interspaces. The blood pressure was 105/65 mm. of mercury.

Laboratory Data. The red blood cell count was 4.19 millions; hemoglobin, 13 gm. and white blood cell count 7700. The blood Wassermann test was negative. The electrocardiogram showed left axis deviation. Roentgenogram of the chest (Fig. 8) showed an area of lessened density in the right lung extending from the fifth posterior interspace to the eighth. This

* This patient was kindly referred to us by Dr. Jacob D. Goldstein.

area was about 8 cm. in diameter and suggested a localized area of emphysema. In the lower portion of the lung there were areas of infiltration from the level of the ninth posterior rib to the base. There were increased linear markings in the lower half of the left lung. The costophrenic angles were slightly hazy. There was some enlargement of the heart in the region of the left ventricle. Four additional roentgenograms taken during a period of 2 years showed no change in these conditions, except the shadows in the right lower lung became more dense.

Clinical Diagnoses. Emphysematous bullæ; rheumatic heart disease with aortic insufficiency.

Methods. The methods employed in this investigation have been amply described in previous communications from this clinic.[5,7,11,12]

	C.D. A	C.D. B	C.D. LYING	C.D. SITTING	A.W. LYING	J.L. LYING	E.W. LYING	R.W. LYING	J.D. LYING	J.D. SITTING
RESIDUAL AIR / TOTAL CAPACITY X 100, %		67		80	68	52	52	50	42	42
MID CAPACITY / TOTAL CAPACITY X 100, %		74		86	76	73	67	67	62	59
% OF PREDICTED, LYING	A	B								
TOTAL CAPACITY	45	74			55	58	73	97	91	
VITAL CAPACITY	20	33			21	37	46	65	95	
RESIDUAL AIR	123	203			145	117	155	197	156	
ARTERIAL BLOOD										
CO_2 CONTENT, VOL. %			54.5	55.3	48.2	62.0	54.0	42.2	–	
O_2 SATURATION, %			83.8	74.3	82.1	79.7	91.0	95.5[x]	–	
HEMOGLOBIN PER 100 cc., GMS.			16.1	17.8	15.8	15.2	13.5	14.4	14.8	
AREA MAXIMUM EXPIRATION / AREA MAXIMUM INSPIRATION, %			89.1	94.6	–	91.8	82.5	71.0	77.9	

x HYPERVENTILATED

FIG. 9.—The pulmonary capacity in cases of emphysematous bullæ and congenital cystic disease of the lungs. Each case is represented by two columns, the left-hand column designates the predicted value while the right one the observed value. The black area represents the residual air while the white space above the vital capacity. "A" under C. D. represents the values when they are predicted from the total area of the chest, including the area of the cysts, while "B," the values when the area of the cysts is not included in the prediction.

Results. Details of the measurements of the pulmonary capacity are given in Figure 9 and Table 1. None of the patients were having paroxysms of bronchial asthma at the time the pulmonary capacity was determined. In 4 instances (C. D., A. W., J. L., E. W.) there was a marked reduction in the total capacity while in the remaining cases this capacity approximated the predicted one. The vital capacity was reduced to an abnormally low level in all instances except one (J. D.) who complained of dyspnea only on moderate to severe exertion. The residual air was increased in all cases, but the increment was not nearly so marked as one would expect in the

presence of such large air-filled cavities. Due to the marked decrease in the vital capacity and the moderate increase in the residual, the latter volume constituted an abnormally high percentage of the total capacity. The values for the ratio $\frac{\text{mid capacity}}{\text{total capacity}} \times 100$ were definitely elevated, in all but 1 case (J. D.). Likewise the tidal volume constituted a much higher percentage of the vital capacity than normally.

TABLE 1.—CARDIORESPIRATORY OBSERVATIONS ON A PATIENT WITH LARGE BILATERAL PULMONARY CYSTS.

Case C. D. No. 52358.	Nov. 14, 1933.		Nov. 15, 1933.	Nov. 18, 1933.	Nov. 24, 1933.
	Lying.	Sitting.	Lying.	Lying.	Lying.
Total capacity, liters	2.83	4.26	2.46	2.55	3.17
Vital capcity, liter	0.94	0.86	0.76	0.84	0.98
Mid capacity, liters	2.09	3.66	1.86	1.89	2.35
Complementary air, liter	0.74	0.60	0.60	0.66	0.82
Reserve air, liter	0.20	0.26	0.16	0.18	0.16
Residual air, liters	1.89	3.40	1.70	1.71	2.19
Ratios:					
Residual air/Total capacity × 100,%	66.8	79.8	69.1	67.1	69.1
Mid capacity/Total capacity × 100, %	73.9	86.0	75.6	74.1	74.1
Tidal volume/Vital capacity × 100, %	43.6	62.8			
Oxygen consumption per min., cc.	240.0	308.0			
Tidal air:					
Carbon dioxide, %	2.94	3.19			
Oxygen, %	17.11	17.00			
Nitrogen, %	79.95	79.81			
Ventilation per minute, liters	6.84	9.93			
Respiratory rate	17.0	20.0			
Tidal volume, cc.	410.0	540.0			
Alveolar air:					
Carbon dioxide, %	5.43	6.21			
Oxygen, %	13.52	12.48			
Nitrogen, %	81.05	81.31			
Venous pressure, mm. H_2O	100, left				100, left 85, right
Blood velocity, seconds	....	...	...	...	20.5
Air removed from cysts:					
Carbon dioxide, %	...	...	8.36	7.65	
Oxygen, %	....	...	7.61	7.79	
Hematocrit, %	48.7				
Red blood cells, millions	6.41				
Hemoglobin, gm.	16.88				
Viscosity	5.8				

The alterations in the pulmonary capacity are strikingly accentuated on assuming the sitting position (Fig. 9, C. D.). The total capacity and residual air were markedly increased and the patient utilized 62.8% of his vital capacity during each respiration. Accompanying these changes in the volume of the lungs, the oxygen consumption per minute and the respiratory rate were augmented.

Likewise there was an increase in the carbon dioxide percentages of the expired and alveolar air. Change of posture affected several other measurements. In the supine position the excursions of the diaphragm were normal in type, while in the upright position they moved paradoxically, *i. e.*, during inspiration they ascended and *vice versa*. The oxygen saturation of the arterial blood decreased from 84% in the lying to 74 in the sitting posture. Likewise the expansion of the chest was markedly diminished in the upright position. Although the alveolar ventilation was greatly impaired in the lying position, while sitting the abnormalities were greatly intensified and dyspnea was more acute.

Roentgenographic Measurements. The size of the chest was larger in this group of cases (18.1 to 23.8 liters) than that of normal men of the same age group (average 15 liters). The shape of the chest was definitely altered. The anteroposterior diameter was greater than normal, thereby increasing the ratio $\frac{\text{depth}}{\text{width}} \times 100$. Likewise the height of the pulmonary fields more closely approximated their width (Table 2). The ability to expand the chest was greatly diminished in all instances, as indicated by the excursions of the diaphragms, lateral movement of the chest, rib rotation and the ratio $\frac{\text{area at maximum expiration}}{\text{area at maximum inspiration}} \times 100$ (Table 2).

TABLE 2.—ROENTGENOGRAPHIC MEASUREMENTS.

	Normal (av. values).	C. D.		A. W.	J. L.	E. W.	R. W.	J. W.
		Lying.	Sitting.	Lying.	Lying.	Lying.	Lying.	Lying.
Excursion of diaphragm, cm.:								
Right	6.0	1.6	P	..	0.5	2.6	5.8	4.3
Left	6.0	1.5	P	..	0.7	3.2	5.0	5.1
Transverse expansion of chest, cm.	2.9	1.1	1.3	..	1.0	1.9	2.8	2.3
Area of pulmonary fields, cm.:[2]								
Maximum inspiration	..	824.0	886.0	939.0	899.0	915.0	769.0	629.0
Maximum expiration	..	734.0	838.0	..	825.0	755.0	547.0	490.0
Ratio:								
$\frac{\text{Area maximum expiration}}{\text{Area maximum inspiration}} \times 100$, %	65.0	89.1	94.6	..	91.8	825.0	71.1	77.9
Rib movement, degrees	19.0	11.0	..	..	19.0	11.0	16.0	20.0
Radiological chest value, liters Inspiration	15.0	..	18.1	22.1	22.0	23.8	16.9	15.1
$\frac{\text{Depth}}{\text{Width}} \times 100$, %	73.0	82.7	..	..	82.7	80.3	75.9	75.4
$\frac{\text{Height}^*}{\text{Width}\dagger} \times 100$, %	69.0	97.5	..	..	103.0	99.3	84.2	77.1

P = paradoxical movement of diaphragm.
* Average height both pulmonary fields at expiration.
† From roentgenogram, expiration.

Analyses of the gaseous content of the arterial blood are shown in Figure 9. The values for the carbon dioxide content were high normal in 3 cases (C. D., J. L., E. W.) while in the remainder there was no deviation from the normal. On comparing oxygen content

and capacity of the arterial blood a low saturation was found in 4 instances. There was no evidence of polycythemia found even in the presence of low arterial saturation. Here again is found a reasonably close correlation between the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$ and the saturation of the arterial blood with oxygen. When the value for this ratio was over 45%, a low value for the oxygen saturation of the arterial blood was found in all but one instance. In this instance the individual, R. W., was observed to hyperventilate his lungs.

In 1 instance, the subject (E. W.) performed 300 kg. per minute for 5 minutes of work on a stationary bicycle ergometer. During this performance he complained of slight breathlessness. The value for the expression $\frac{\text{total ventilation}}{\text{vital capacity}}$ was 61, one slightly above the level of dyspnea previously found for normal individuals, *viz.* 51. Likewise while performing this amount of work the minute ventilation during the final 2 minutes of exercise constituted 88% of his maximum ventilatory power in contrast to the normal average value of 35%. His pulmonary reserve was greatly reduced, *viz.* 29 liters compared with 63 liters for normal individuals.

Discussion. The functional changes referable to the respiratory system in this series of cases are similar to those observed in patients with obstructive pulmonary emphysema.[1,8,10] The most common symptoms were productive cough and dyspnea. The volume of the chest was large and its expansion greatly diminished. The anteroposterior diameter of the chest was increased and the thorax was held at an inspiratory position. The vital capacity was greatly reduced in all instances except 1 (J. D.). The remaining components of the total capacity are at variance with the typical picture seen in cases of obstructive emphysema, in which the total capacity approximates the predicted values and the residual air is greatly increased as is the case in emphysema, while in the cases with cystic lungs the residual air was only slightly increased. The total capacity was markedly reduced. The reduction in the total capacity is probably due to the fact that the accuracy of determining the residual air by the oxygen dilution method is somewhat impaired in the presence of such bizarre changes in the lungs. The mixing between spirometer and lungs is probably not homogeneous at the end of the rebreathing period.[2] It is conceivable that in many of these cases, especially in the instance of C. D., the residual volume does not include the contents of the cysts because of poor ventilation between the tidal air and the gaseous content of the cysts. Pulmonary cysts with gaseous contents are always in communication with the outside air, for, if this were not so, the air would soon be absorbed and the walls collapse. There are several reasons for believing that the ventilation in such cysts is poor. In the case of C. D., at autopsy there was found no large bronchial communica-

tion with the cysts. Due to compression of the adjacent pulmonary tissue the communications were probably small and tortuous. The tension of the carbon dioxide and oxygen of the gas aspirated from the cysts was very similar to that that one would expect of the mixed venous blood of the patient, indicating that the gaseous exchange between the cyst and outside air was minimal. After forcefully rebreathing for 23 seconds a mixture of gas containing 15% acetylene, the gas removed from the cavity of the right lung showed an acetylene percentage of only 0.15. Fluoroscopic examination showed no change in the size of the cavities during respiration. Likewise no change in the area of the cavities, between maximum inspiration and expiration could be found on a doubly exposed roentgenogram when measured by means of an accurate planimeter. One would suppose then that during the rebreathing period the contents of the cavity was not measured. If the volume of the cysts were included in the volume of the air remaining in the thorax at the end of maximum expiration, the residual air should be very much increased, resulting in a normal or high volume for the total capacity. The factors responsible for the marked alterations in the pulmonary capacity and for the arterial anoxemia have been described elsewhere and need not be stressed here.[1,7,8,10]

A point of interest in the case of C. D. was the observation that the patient was worse when he was in the sitting position than when he lay flat. The increased respiratory distress on assuming the upright position may readily be explained on a mechanical basis. In contradiction to normal individuals the vital capacity decreased on assuming the upright posture, resulting in an increase in the ratio $\frac{\text{tidal volume}}{\text{vital capacity}} \times 100$. Consequently, the pulmonary reserve was reduced and each inspiration required greater effort to effect an adequate tidal volume in the sitting as compared with the recumbent posture. The factor responsible for the diminution in the vital capacity was probably the paradoxical movements of the diaphragm. On changing from the lying to the sitting position the pressure within the cyst became more positive. This decrease in the vital capacity with change in posture has been noted in about half of the cases with marked obstructive emphysema that we have investigated. By assuming the upright posture the alveolar ventilation was further impaired as evidenced by the increase in the carbon dioxide content of the arterial blood and the increased anoxemia. A similar case was reported by Means[15] in his monograph on "Dyspnœa." The patient had severe dyspnea without orthopnea. At autopsy, he was found to have a lymphoma of the mediastinum. The author believed that the major portion of the dyspnea was mechanically produced.

In Table 3 the cases are arranged according to their disability as rated by interrogating the patients. There was a fairly close corre-

lation between the ease with which shortness of breath was produced and the various components of the pulmonary capacity, anoxemia and expansion of the chest. It is of interest to note that the lesions seen on the roentgenogram of case J. D. are similar to, although less extensive than those of C. D. The former patient had little or no disability while the latter was dyspneic at rest. This supports our contention that the roentgenographic lesions do not always parallel respiratory function and that functional tests are necessary in many instances to properly evaluate disability.

TABLE 3.—RELATIONSHIP OF DYSPNEA TO CERTAIN RESPIRATORY MEASUREMENTS.

Case.	Dyspnea.*	Vital capacity, % of predicted.	Residual air / Total capacity × 100.	Mid capacity / Total capacity × 100.	Tidal volume / Vital capacity × 100.	Oxygen saturation, arterial blood.	Area max. expiration / Area max. inspiration × 100.	Depth / Width × 100.
			%	%	%	%	%	%
J. D.	+	95	42	62	15	..	78	75
R. W.	++	65	50	67	25	95.5	71	76
E. W.	++	46	52	67	28	91.0	83	80
J. L.	++	37	52	73	27	79.7	92	83
A. W.	+++	21	68	76	47	82.1		
C. D.	++++	20	67	74	44	83.8	89	83

* ++++ = at rest; +++ = on slight exertion; ++ = on moderate exertion; + = on severe exertion.

Dyspnea in individuals with congenital cystic disease of the lung and emphysematous bullæ may be readily explained by mechanical impairment of the respiratory bellows. In other words, the lungs are unable to supply an adequate amount of oxygen to the tissues. In 1 case (C. D.), in order to meet the demands of the body at rest, respiratory effort was close to the maximum and dyspnea was so severe that muscular exertion was impossible. In several of the other cases (A. W., J. L., and E. W.) the ventilatory reserve was greatly reduced consequently slight increase in the demand of the body for oxygen caused dyspnea.

The nature of the pulmonary cysts in these cases demands a brief discussion. Cystic disease of the lung is usually classified under two main groups, the congenital and the acquired forms.[3] Under both headings one may find the lesions to be either unilateral or bilateral and solitary or multiple. Either may contain fluid or air. When round shadows are found in the roentgenogram of the chest, a whole host of conditions creeps into the differential diagnosis. The many possibilities have been recently enumerated and discussed by various observers and need not be stressed here.[4,17,19,21] *et al.*

The question that arises from the study of this group of adults is, Are these air-filled cysts congenital in nature and develop later in life to produce symptoms or are they the result of acquired chronic changes in the bronchial tree and pulmonary parenchyma? The patients in this series had certain things in common; (*a*) all had a history of respiratory infection, (*b*) all but 1 (J. D.) had symptoms of respiratory insufficiency, (*c*) in all instances there was pulmonary emphysema, fibrosis or both, and (*d*) half the patients had paroxysms of bronchial asthma. It is particularly difficult from a clinical standpoint to understand just what part chronic pulmonary infections play in this picture. It is well known that bullæ producing round shadows on the roentgenogram may be the result of marked emphysematous changes in the lungs. Several authors[9,13,16,20] have reported such cases. On the other hand, proven cases of congenital cystic disease have been found in very old individuals, who had no symptoms referable to these changes throughout their whole life. Likewise congenital defects may remain silent until later in life when some pulmonary infection or disorder is superimposed.

In the first patient (C. D.), who presented the large bilateral cysts, so-called balloon cysts, there was a great deal of discussion concerning the nature of the cysts even after careful pathologic examination. The following anatomic facts appear to support the proportion that in this case the lesions were acquired; pigmentation of the compressed alveoli composing the wall of the cyst and the numerous large emphysematous bullæ in the peripheral portions of the lower lobes. Many of these smaller bullæ had the same anatomic configuration that the larger cysts had. In addition, this patient was exposed to a considerable amount of dust over a long period of years. It is not uncommon to find a certain amount of fibrosis, bronchial infection and varying degrees of emphysema in men who worked in the mines for a great many years. Prior to this patient's army life there was no history of disability. The history of gradually increasing disability indicates that the process was gradually progressing and that the cysts were increasing in size over a period of years. One would expect then that the bronchial communications had a valve-like action, a one-way mechanism at the orifices. However, on the other hand, one may argue that the patient had the defect since birth and that the various superimposed factors (dust and bronchial infection) simply produced the valve-like action in the bronchial tree, causing the cysts to increase in size and other portions of the lung to be compressed.[18] In either case, the end result may be the same. This case is very similar to those reported by Wilson,[20] Karan and Haymaker[13] and Jacobaeus.[9] These authors concluded that the cysts were not congenital but developed during life from changes in the bronchial tree.

Although the symptoms and signs of respiratory insufficiency are lacking in the sixth case (J. D.), from a roentgenographic viewpoint

it is very similar to that of the first patient (C. D.). The process is unilateral and much less advanced, but the roentgenograms have similar characteristics. Post-pneumonic alterations of the lung may have been the original disease process, leading to breakdown of the alveoli, resulting in compression of the lower and middle lobes by the expanding emphysematous bullæ in the upper lobe. The ill defined wall and the scattered lacy network throughout the cysts suggest a cavity formed by breakdown of the pulmonary parenchyma rather than congenitally formed cysts.

The third patient (J. L.) had paroxysms of bronchial asthma for 14 years. The roentgenograms as well as measurements of the residual air indicate that he had well marked obstructive pulmonary emphysema. It seems reasonable to assume that the areas of decreased density as seen on the roentgenogram of the chest, is due to breakdown of the alveoli from bronchial obstruction and may be classified as emphysematous bullæ rather than congenital cystic disease of the lung. The fifth patient (Fig. 7) shows similar changes in the left upper lobe. The history of asthma, however, was of only 3 years' duration. In the fourth case (R. W.) the history of bronchial infection, bronchial asthma and exposure to dust containing some silica over a period of years and the ill defined outline of the area of increased radiability of the lungs are sufficient evidence to make the diagnosis of obstructive emphysema and emphysematous bullæ.

The second patient (A. W., Figs. 5 and 6) has multiple cysts and on the roentgenogram the cavities are irregularly arranged, are spherical, have sharply defined outlines, with little evidence of pulmonary infiltration between the walls of the cysts. These characteristics are considered by many to be the criteria for congenital cystic disease of the lung.

It appears then from a clinical viewpoint it is often impossible to distinguish between congenital cystic disease of the lung and emphysematous bullæ. The multiple cysts which are more commonly found in adults as a rule cause no marked disability unless there is a superimposed infection and are usually discovered accidently later in life. When annular cavities with poorly defined walls, which show no pulmonary markings but fine linear strands traversing the cystic space associated with respiratory disability and pulmonary emphysema or fibrosis, emphysematous bullæ should always be included in the differential diagnosis.

Summary and Conclusions. Six patients with air-filled pulmonary cavities were investigated from a functional viewpoint. In all cases the pulmonary capacity was determined, roentgenographic measurements were made and the arterial blood was analyzed for its oxygen and carbon dioxide content. In 1 case the ventilatory response during exercise was determined. One patient (C. D.) with large bilateral pulmonary cavities came to necropsy and the

pathologic lesions are described. From the aforementioned studies the following conclusions may be drawn:

1. In half of the cases the total capacity, as well as the vital capacity, is reduced while the residual air is only slightly increased. Evidence has been produced which indicates that in these 4 cases the volume of the cysts is not included in the residual air. This accounts for the small increase in the residual air and the marked decrease in the total capacity. In the remaining cases the alterations in the pulmonary capacity are typical of those of obstructive pulmonary emphysema, *i. e.*, a marked decrease in the vital capacity with a corresponding increase in the residual air, resulting in a normal value for the total capacity.

2. The ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$ is increased in all cases.

3. The volume of the chest is larger in this series of cases than in a group of normal men of the same age group. The shape of the chest is characteristic of obstructive emphysema, *i. e.*, barrel-shaped. The ability to expand the chest in all cases is markedly diminished.

4. There is a slight retention of carbon dioxide in 3 cases, as evidenced by the carbon dioxide content of the arterial blood. There is a certain degree of anoxemia in 4 of the cases. There is a reasonable close correlation between the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$ and the oxygen saturation of the arterial blood.

5. The pulmonary reserve is reduced in cases of emphysematous bullæ and congenital cystic disease of the lung.

6. The degree of dyspnea is closely related to the decrease in vital capacity and expansion of the chest and to the increase in the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$.

7. Dyspnea in such cases may be readily explained by the mechanical impairment of the respiratory bellows.

8. The nature of the pulmonary air cysts in this series has been discussed.

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THE EFFECTS OF LARGE DOSES OF INSULIN ON BLOOD HYDRATION IN MAN.*

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The use of insulin in the treatment of schizophrenia affords good opportunity for the study of phenomena associated with hypoglycemia produced by insulin in relatively healthy men and women. Clinical observation suggests that marked losses of water and electrolytes occur through sweating and hyperventilation when hypoglycemia is allowed to persist for several hours. Work with animals, while there has been some disagreement,[5] in general supports the results of Drabkin and Edwards[3] and Drabkin[2] who reported that insulin in amounts of 20 units per kg. of body weight brings about profound hemoconcentration in dogs. Chaikelis,[1] using doses up to 1 unit per kg. in rabbits, found moderate anhydremia, as shown by increases in plasma solids and in red cell count and hemoglobin; he attributes the last two findings to splenic contraction. A review of the literature to 1934 appears in Chaikelis' article. More recently, Drabkin and Ravdin[4] have reported that anhydremia is a factor in the cycle of events leading to convulsions in severe hypoglycemia produced by insulin in dogs.

Since data on man are, so far as we know, incomplete, and the quantity of insulin necessary to produce coma in man is far below the dose used by Drabkin in dogs, it was felt that the effects produced by less abnormal quantities of insulin in man might be of interest. A study of blood hydration in artificially produced insulin hypoglycemia was therefore undertaken.

Methods. The subjects of this study were 12 patients at the Philadelphia General Hospital.† Of these, 10 were diagnosed as schizophrenics, 2 as manic-depressives. Prior to acceptance for the insulin treatment, electrocardiograms, urea clearances and basal metabolic rates (on coöperative patients) were obtained. These studies, repeated at intervals, insured that the subjects in this series, men and women in the first third of life, were in reasonably good physical health.

Fifteen experiments on 12 patients (8 men and 4 women) and 2 control experiments on 2 men are reported. The following procedure was used. Insulin, in a dose found previously to produce coma in the subject studied, was given subcutaneously between 7 and 8 A.M. Coma usually developed 2 to 3 hours after injection and was terminated 1 to 2 hours after onset by intravenous injection of 50 or 100 cc. of 33% glucose. Food was withheld from the patient for 10 hours before the insulin injection; no food or fluid was given during the experimental period. No restriction of food or fluid

* Awarded the annual Charles W. Burr Prize by the Medical Board of the Philadelphia General Hospital.

† Drs. Burr, Hadden and Strecker were kind enough to allow these observations to be made on patients on their services.

after termination could be enforced under the circumstances. Blood samples were drawn at intervals during the coma and after termination, and compared with a fasting sample taken just before insulin was given. At least 5 samples were secured in each experiment.

Hemoglobin, red cell volume and refractive index of the plasma were determined in duplicate or triplicate. Venous blood was drawn as uniformly and rapidly as possible into a dry syringe and 4 cc. mixed with 8 mg. of dry sodium oxalate in a small test-tube. Precautions were taken to avoid hemolysis by gentle handling, and evaporation by keeping the rubber-corked tubes in a moist chamber between manipulations. The tubes were inverted 20 to 30 times to ensure thorough mixing. Hematocrit values were determined in Wintrobe tubes after centrifuging all samples in a single experiment together for 30 minutes at 2200 r.p.m. (centrifuge radius 15 cm.). Since the same concentration of sodium oxalate was used in all samples, its effect on cell volume would not influence comparison between them. A dipping refractometer was used for the refractive indexes, all readings being made at a temperature of 19° C. Hemoglobin was determined by diluting 0.5 cc. of blood to 50 cc. with N/10 HCl in a volumetric flask; after standing 24 hours, the acid hematin solutions were compared colorimetrically, using the fasting blood hematin solution as a standard. One or more blood sugar determinations (modified Folin and Wu method) were done in each experiment.*

All patients were weighed before being given insulin and shortly after termination of the coma.

The dosage of insulin varied from 0.75 to 3.24 units per kg. of body weight. The smallest amount given was 43 units, the largest 245 units.

Results. Eight of the 12 patients showed marked sweating during coma, 4 remained relatively "dry." This difference in response has been previously noted by Sakel[7] and thought to have prognostic significance. The blood sugar levels in all subjects shortly before termination ranged between 15 and 30 mg. %. No relationship was found between the weight or other characteristics of the patient and the dose necessary to produce coma.

Refractive indexes of the plasma were secured in all 15 experiments, hematocrit determinations in 14 and hemoglobin values in 6. The results are summarized in Table 1.

TABLE 1.—CHANGES IN THE BLOOD OF SUBJECTS IN THE THIRD TO FOURTH HOURS OF INSULIN HYPOGLYCEMIA.

Determination.	Number of experiments.	Number showing increase.	Range of increase.	Number showing decrease.	Range of decrease, %	Number showing no change.
Red cell volume .	14	10	4–12%	2	5	2
Hemoglobin . .	6	5	7.8–9.3%	0	0	1
Refractive index of plasma . . .	15	12	0.00037–0.00256	0	0	3

The majority of subjects, as seen in Table 1, showed after 3 to 4 hours of insulin hypoglycemia a moderate increase in red cell volume and hemoglobin. This result might be produced by an increase in circulating cells following splenic contraction, as was concluded by Chaikelis[1] to be the case in rabbits after the injection

* Miss E. Fortunato kindly performed the blood sugar determinations.

of insulin. In our material, however, the rise in hemoglobin and red cell volume was accompanied by increase in plasma refractive index, allowing us to consider loss of water from the blood to be the basis of the changes found.

TABLE 2.—SUMMARY OF MAXIMUM CHANGES IN 3 TO 4 HOURS OF INSULIN HYPOGLYCEMIA.

1	2		3	4	5	6	7	8	9	10	11
No.	Name and sex.		Date, 1937.	Air temperature, °C.	Amount of insulin in units.	Amount of insulin, units per kg.	Weight loss in %.	N_D fasting and highest values 1.3—,	Maximum changes before termination in % of fasting value.		
									Plasma protein.*	Hematocrit.	Hemoglobin.
1	J. D.	M	Oct. 14	22.5	43	0.75	1.2	4947 4966	2.2†	1.9†	7.8†
2	M. S.	F	Aug. 24	22.5	55	1.19	2.9	4895 4966	6.2†	3.3†	
3	J. L. (1)	M	Sept. 8	..	100	1.28	4.5	4973 5047	5.4	4.2	
4	J. L. (2)		Sept. 4	28.0	100	1.33	3.3	4862 5068	16.0	7.0	
5	J. L. (3)		Oct. 6	27.6	110	1.39	..	4940 5105	12.4	5.2	8.3
6	C. R.	M	Aug. 17	28.0	90	1.61	3.9	4869 5036	12.9	12.0	
7	G. N.	M	Oct. 22	23.7	120	1.62	2.4	4823 4947	10.4	0	0
8	M. C. (1)	M	Sept. 15	19.5	142	1.66	0‡	5031 5068	2.6	4.0	
9	A. Z.	F	Aug. 30	28.0	95	1.74	0.5‡	4903 4954	3.8	4.2	
10	E. H.	F	Sept. 2	28.0	105	1.85	1.6	4851 4851	0	1.5	
11	J. N.	M	Aug. 13	..	180	2.30	Profuse sweat	4761 5017	22.0	6.7	
12	M. K.	F	Oct. 16	22.0	100	2.49	0‡	4862 4951	7.1	5.0	8.7
13	C. M.	M	Sept. 21	22.0	150	2.53	1.15	4940 5162	16.5	8.0	8.5
14	M. C. (2)		Oct. 25	22.0	245	2.56	0.7‡	4906 5095	14.5	7.2	9.3
15	A. B.	M	Aug. 20	32.0	190	3.24	Profuse sweat	4951 5125	12.75		

* Calculated from change in refractive index. See text.
† Decrease to fasting or below fasting level before termination.
‡ "Dry shock."

When maximum figures in individual experiments (presented in some detail in Table 2) are compared, it is noted that the refractive index (N_D) changes fall into two groups. In one (Cases 3, 6, 8, 9 and 12) the increase in N_D, when translated into terms of plasma

protein concentration,[6] corresponds fairly closely to the change in red cell volume and hemoglobin. Thus, for example, in Experiment 12, N_D rose from 1.34862 to 1.34951, corresponding to a change in plasma protein concentration of 7.1% from the fasting level. At the same time, the hemoglobin content increased by 8.7%. In the second group (Cases 4, 5, 11, 13, 14), figures derived from the refractive index show a water loss from the blood of 1.5 to 3 times the magnitude inferred from the hemoglobin and hematocrit values. Lack of direct plasma protein determinations does not allow us to rule out the possibility that in this set of experiments entrance into the plasma of material other than protein may have altered the refractive indexes over and above the increase produced by anhydremia. This reservation should be kept in mind when considering Column 9 in Table 2, which gives the protein values calculated from the refractive indexes. In any case, we feel that the similar direction of the results obtained indicates an increase in concentration of the blood through loss of water rather than addition of cells. To illustrate the first group of experiments, Figure 1 (Case 12) is appended; the other group is represented by Figure 2 (Case 13).

In the first 3 hours of the insulin effect, the increase in hemoglobin exceeded the increase in red cell volume (by 2 to 7% in 5 experiments), so that there was evidently loss of water from cells as well as from plasma with consequent shrinkage of erythrocytes. After 3 hours, the hematocrit values rose more rapidly to parallel, though not necessarily to reach, the hemoglobin levels (Figs. 1 and 2).

Four experiments presented some exceptions. In Cases 1 and 2, no stable change was produced probably because the quantities of insulin used were quite small, 0.75 and 1.19 units per kg. respectively. In both cases there appeared a transitory small increase in red cell volume and refractive index in the first 3 hours, followed by a fall within the next hour. A parallel increase in hemoglobin, greater than the change in red cell volume, was noted in Case 1.

One patient (Case 7) showed no appreciable change in hemoglobin or red cell volume in 4 hours when 1.62 units per kg. were administered; however, his plasma refractive index increased from 1.34823 to 1.34947 in the same time. Another subject (Case 10), a woman, given 1.85 units per kg., showed no significant change in red cell volume or refractive index within 4 hours. These patients differed from the others in that they presented manic-depressive rather than schizophrenic symptoms.

Weight losses, ranging from 0 to 4.5% of the body weight, were observed following the injection of insulin. The greatest losses were noted in the experiments conducted during the summer, when the sweating reaction produced by insulin in most of the patients was intensified by the high air temperature (28° to 32° C.) and humidity. It will be noted, however, in Table 2, that insulin pro-

duced concentration changes independently of air temperature. Furthermore, weight loss was not invariably associated with the effect of insulin. Thus the 4 patients (Cases 8, 9, 12, 14) who exhibited a "dry" reaction, lost little or no weight. Two of them (Cases 12 and 14), given about 2.5 units per kg. at 22° C., showed increases in hemoglobin of about 9% and in refractive index of 0.00087 and 0.00189 respectively; the other 2, given 1.7 units per kg., showed slight change. The change in blood concentration may be

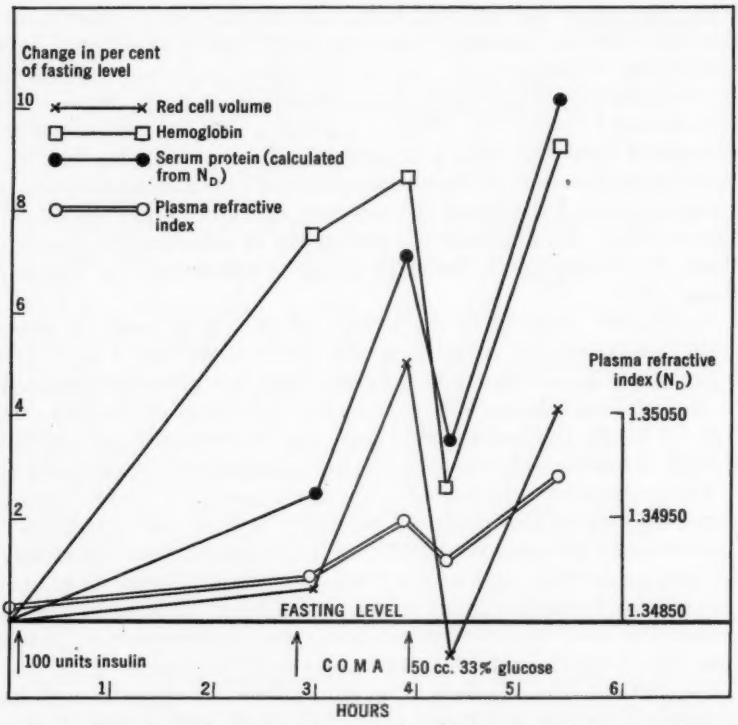

FIG. 1.—Experiment 12. Case M. K., white, female, aged 18 years. 100 units insulin (2.49 units per kg.). Air temperature, 22° C. "Dry shock," no weight loss. Graph illustrates experiment in which the increase in serum protein, calculated from change in refractive index, agrees fairly closely with the rise in hemoglobin.

due partly to loss of water through excessive sweating in some cases; in others, diuresis, actually observed repeatedly in 2 patients after the administration of insulin, or shifts of water within the body, or a combination of all these, may be responsible.

The phenomena involved are too complex to expect a constant relationship between the magnitude of insulin dose and the reaction produced; however, larger doses apparently produce greater effects. A stable change was not effected with doses below 1.3 units per kg.

(Experiments 1 and 2), while above 2 units per kg. maximum increases were obtained. Subject M. C., refractory to insulin, exhibited more marked changes at 2.56 units per kg. (Case 14) than he did at 1.66 units per kg., a dose insufficient to produce profound coma in his case. The variability of response to nearly the same amount of insulin by the same patient is illustrated by Subject J. L. (Cases 3, 4, 5).

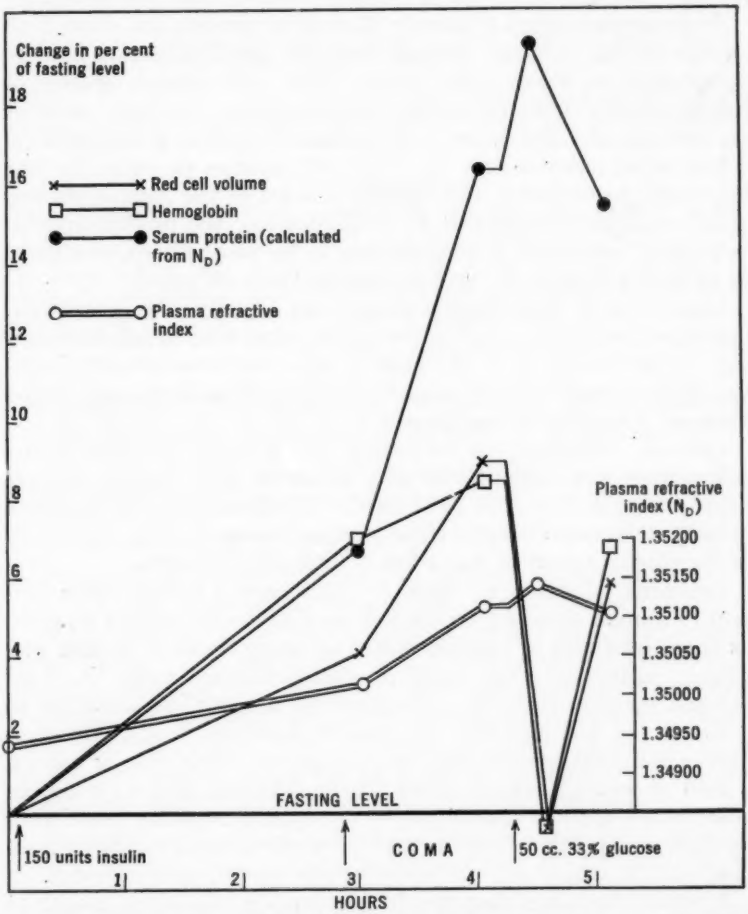

FIG. 2.—Experiment 13. Case C. M., white, male, aged 33 years. 150 units insulin (2.53 units per kg.). Air temperature, 22° C. Profuse sweating, weight loss 1.15% of fasting weight. Graph illustrates case in which the serum protein increase, calculated from change in refractive index, exceeds the rise in hemoglobin.

Changes After Termination. One or more samples of blood were taken at varying times after termination of coma by 50 or 100 cc. of 33% glucose intravenously, in 12 experiments on 10 subjects.

Fifteen to 40 minutes after termination, 6 of 7 samples showed a fall in hemoglobin and hematocrit red cell volume from the pre-termination values ranging from 1 to 8% of the fasting levels. In Experiment 1, a sample taken 28 minutes after termination showed an increase of 16.9% in red cell volume and 13.3% in hemoglobin; the plasma refractive index increased by 0.00251, a proportionate rise. This patient received the smallest dose of insulin (0.75 unit per kg.), but otherwise did not appear to differ from the others.

Five samples taken 1 hour or later after termination showed no change or only a slight increase from the pre-termination level in hematocrit or hemoglobin values. One such sample showed a further decline from an earlier post-termination fall and another an increase of 7.3% in red cell volume in terms of fasting level 1 hour after termination. In 5 out of 7 samples taken in the first hour after termination, the refractive index of the plasma showed a fall ranging from 0.00041 to 0.00126 below the pre-termination value; and in 6 out of 7 samples taken in the second hour, no change or an increase from the pre-termination value occurred.

Inspection of these figures shows that, usually, the hematocrit, hemoglobin and plasma refractive index values tend to fall, occasionally to the fasting level or below it, after termination with intravenous hypertonic glucose, and then rise again to their coma values during the next hour (see figures).

Controls. Changes not exceeding 2% in either direction in red cell volume and hemoglobin were observed in 2 fasting subjects kept in bed for 4 hours at 22° C. under conditions reproducing those in the insulin experiments. The greatest change in refractive index of the plasma observed was a fall of 0.00023 in 4 hours.

Comment. Judging by these results, changes in the water content of human blood under the influence of insulin are not as great as those observed in animals with the larger doses of insulin previously employed. The systemic disorganization noted in dogs[3] did not occur in man when insulin in an amount just sufficient to induce coma was injected. It appears, however, that in the complex of reactions constituting the response to a large dose of insulin, a shift of water from the blood stream into the tissues occurs, an effect which may be manifested by the typical sweating reaction or by diuresis; and that both the shift of water and the sweating reaction may be absent without affecting the development of coma.

It should be noted that the changes reported are large enough to affect concentrations of electrolytes as well as non-electrolytes of the blood, so that concentration changes should be considered in studies of blood during insulin coma.

Summary. 1. The effect of insulin, administered in amounts sufficient to produce coma, upon the water content of the blood in 12 human subjects was studied.

2. Injection of 1.28 units per kg. of body weight or more caused

maximum increases above the pre-insulin values in erythrocyte volume of 4 to 12%; hemoglobin, 7 to 9%; plasma refractive index, 0.00037 to 0.00256, in 3 to 4 hours.

3. These changes were not always associated with marked sweating or loss of weight and cannot be entirely explained by external water loss, nor do they invariably accompany insulin hypoglycemia.

4. Attention is called to the importance of considering water concentration changes in studies of blood in insulin coma.

The author wishes to express his gratitude to Dr. S. DeW. Ludlum for the use of the laboratory in the Psychopathic Division at the Philadelphia General Hospital; to Dr. J. G. Reinhold for the suggestion responsible for this investigation and advice during its progress; and to Dr. H. Freed, in charge of the insulin treatment of the patients studied. The coöperation of Miss D. S. Grove, R.N., in the management of the patients is gratefully acknowledged.

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HYPERPARATHYROIDISM DUE TO PARATHYROID ADENOMA, WITH DEATH FROM PARATHORMONE INTOXICATION.

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Since Mandl's[12] demonstration in 1925 of the causative relationship between parathyroid tumors and osteitis fibrosa cystica, the clinical picture of hyperparathyroidism has been greatly augmented and clarified.[1] Several studies of acute parathormone poisoning of dogs are on record,[2,3a,8] but no instance of death from parathormone poisoning in man has been observed clinically. It is the purpose of this communication to fill this gap in the natural history of hyperparathyroidism by recording an instance of death resulting from parathormone intoxication due to parathyroid adenoma.

Case History. A white housewife of 49 was admitted complaining of pain in the right chest and a feeling of tiredness. She had been admitted to another hospital on two occasions; first in 1926, with pyelitis, and the second time, in 1932, when a diagnosis of hydronephrosis on the right, with calcareous deposits in both kidneys, was registered. At this time blood chemical studies revealed the following: Ca, 12 mg. %; sugar, 100 mg. %; urea nitrogen, 30 mg. %; creatinine, 2 mg. %; and N.P.N., 50 mg. %. Phenolphthalein excretion: 35% in 1 hour with a total of 43% in 2 hours. The urine showed a few hyaline casts, many leukocytes, and a few red cells.

Roentgen ray pictures of the kidneys, taken in 1932, show the diffuse mottling of the parenchyma which is now regarded as characteristic of hyperparathyroidism.

From 1932 until May, 1936, she had been well, with a good appetite and doing her own housework. She then began to have dull pain under the right shoulder blade which persisted off and on until May, 1937, when she developed a pain in the anterior chest on the right, about the level of the third rib. During June, July and August, 1937, she became very weak, remaining in bed at one time for 2 weeks, and, despite an unfailingly good appetite, she constantly lost weight. During the past 12 months her weight has decreased 30 pounds. She has not been nervous, sleeps well, and has had no pain except in the right chest as described. No polydipsia or polyuria.

Physical examination on September 21, 1937, revealed a small, undernourished, white woman who did not appear at all ill, and who was pleasant, alert and coöperative. Temperature, 38.2° C.; pulse, 120; respirations, 22; blood pressure, 148/90. At the left lower pole of the thyroid there was a round, firm nodule, about 2 cm. in diameter. A rather indefinite mass was felt in the right hypochondrium which was thought to be the kidney. The physical examination was otherwise quite negative. The blood on admission was: erythrocytes, 3,500,000; hemoglobin, 10 gm. (66%); leukocytes, 6200; differential count not abnormal. The specific gravity of the catheterized urine was 1.012, with a trace of albumin and 10 W.B.C. per high-power field. No electrocardiographic study was made.

The correct diagnosis was not suspected until a Roentgen ray plate was made of the kidneys. Dr. Reeves reported: "The kidneys are quite low, and both are filled diffusely with a mottled deposit of calcium, typical of the changes seen in hyperparathyroidism (Fig. 1). All of the bones show generalized loss of calcium."

On the fourth day after admission, the blood chemical findings were as follows: Ca, 20 mg. %; phosphorus, 4.7 mg. %; and refractive index, 1.3492. The nodule at the left pole of the thyroid was now suspected of being a parathyroid tumor, and the patient agreed to an operation. She had been quite cheerful and uncomplaining, but during the next few days became rather depressed and complained a great deal of weakness and pain in the chest.

The blood chemical findings on the seventh admission day were: Ca, 22 mg. %; phosphorus, 4.8 mg. %; phosphatase, 23 Bodansky units; plasma N.P.N., 58 mg. %; total protein, 6.2 gm. %. A phenolphthalein excretion test on September 28 showed 20% excretion of the dye in 30 minutes and a total of 40% in 90 minutes.

Ten days after admission, it was noted that the patient was quite nervous, complained of feeling very weak, and was hoarse. The temperature was 38.5° C.; pulse, 120. The surgical consultant felt it advisable to postpone operation. The patient had had a slight fever daily up to 38° C., but on the last 2 days of life this had increased to 38.5° C. Throughout her stay the pulse was accelerated out of proportion to the fever. The last note on October 2 was as follows: "For the past 48 hours the patient has changed remarkably in her reactions. She has complained of great weakness and nervousness and, in contrast to her former cheerfulness, has been quite tearful. The rise in temperature of the past two days has been attributed to a possible upper respiratory infection. Tonight she complained of generalized aching pain. This morning at about 3 A.M. she called the nurse, who found her gasping for breath and quite cyanotic. Before I could reach the ward she had expired."

A complete *autopsy* was performed and the anatomic diagnosis was as follows: "Cystic and partly calcified and necrotic tumor of the parathyroid gland (lower left pole of thyroid). General intoxication (parathormone) with widespread injury necrosis and calcification of the connective tissue, especially that forming the basement membrane of the parenchymatous

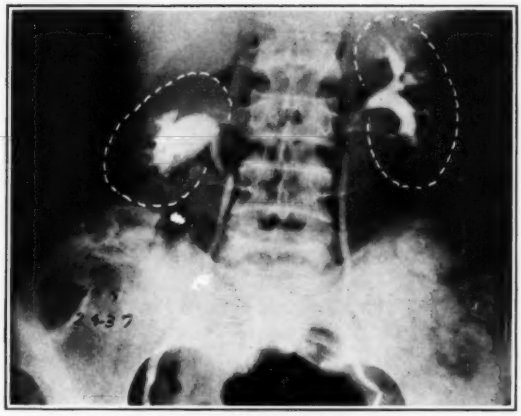

FIG. 1.—The kidney pelves are filled with radio-opaque fluid. The calyces are seen to enclose the papillae, which are outlined by delicately mottled calcium deposits.

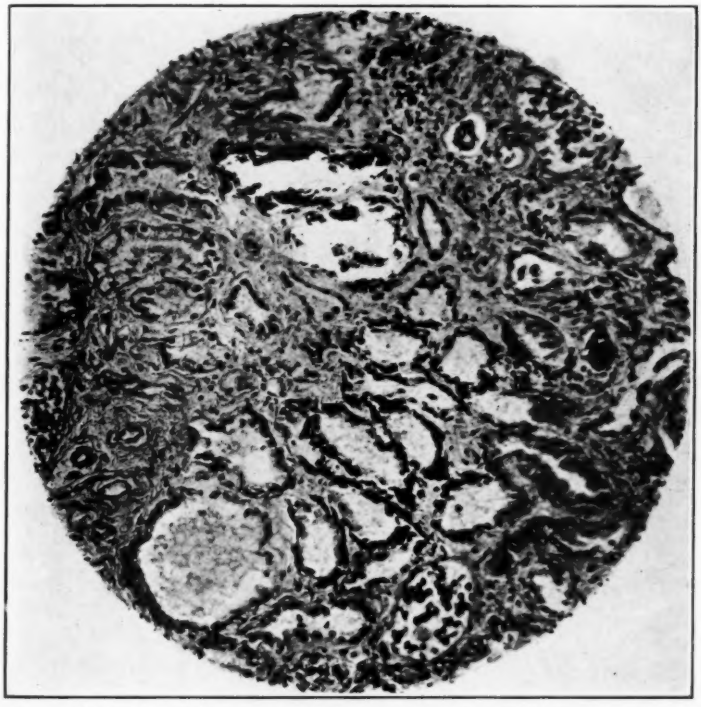

FIG. 2.—Calcification of basement membranes of kidney tubules, with necrosis of epithelial cells.

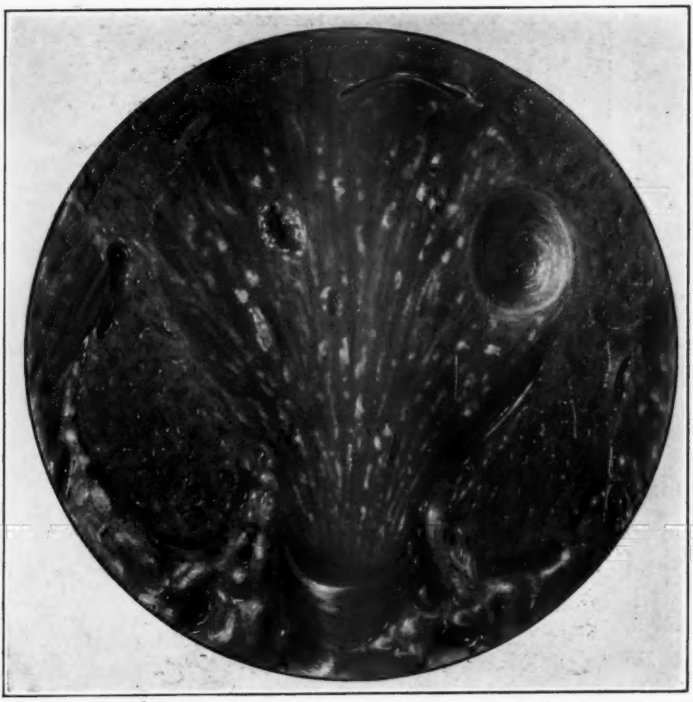

FIG. 3.—Drawing of the pyramidal portion of fresh kidney, showing extensive calcium deposits.

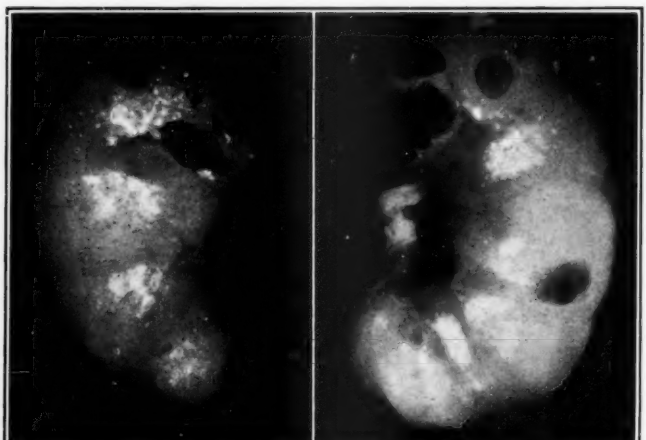

FIG. 4.—Roentgen ray picture of the two halves of one kidney, showing calcium deposits in parenchyma.

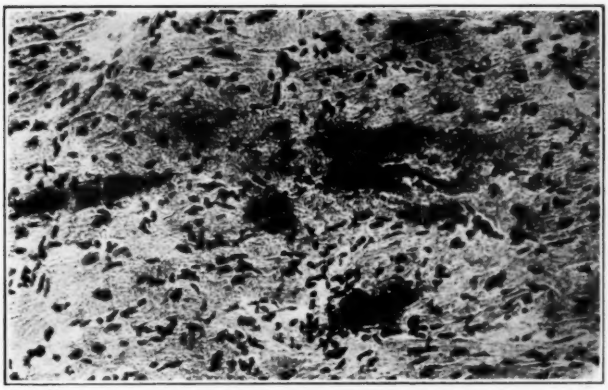

FIG. 5.—Calcification of muscle cells and arteries of the heart. The calcium is seen as fine granules and masses.

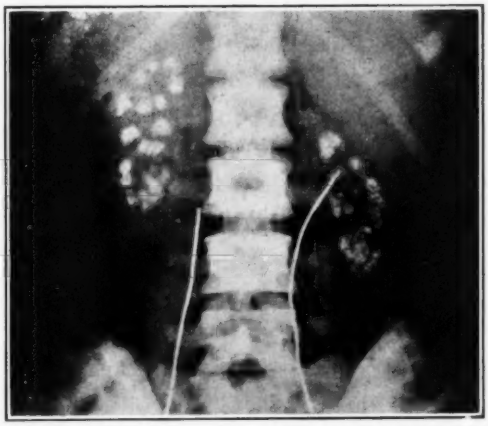

FIG. 6.—Figures 6 and 7 are from two other instance of hyperparathyroidism observed in the Duke Clinic. The delicate rosette-like mottling, due to parenchymatous calcium deposits (nephrocalcinosis) is probably pathognomonic of hyperparathyroidism.

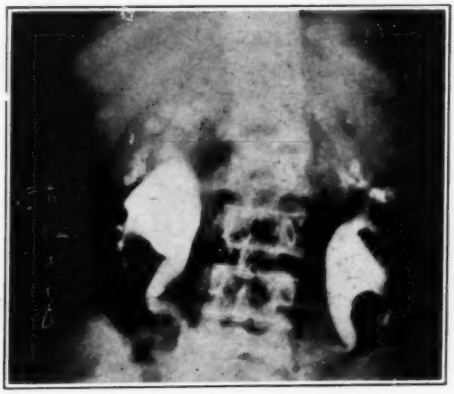

FIG. 7.—Nephrocalcinosis.

organs and the arteries of medium and arteriolar size. Extensive myocardial injury and necrosis. Chronic tubular and glomerular nephritis with extensive medullary calcium deposits. Hepatic focal necrosis."

Calcification was present in the kidneys (Figs. 2, 3 and 4) and myocardium (Fig. 5) to a marked degree, together with widespread evidences of injury to connective tissue throughout all the organs. This was seen most conspicuously in the basement membranes of the parenchymatous organs, associated with cell necrosis and calcification. Calcium deposits were also present in the stomach and lungs to a slight degree. There was widespread calcification of the media of arterioles in the heart, kidneys and lungs.

The autopsy findings in this patient parallel very closely the pathologic changes which Cantarow, Stewart and Housel[2] describe in dogs poisoned with parathormone.

There is no evidence that this patient's death was due directly to the kidney injury which was present; neither the blood chemistry studies nor the symptoms which she presented indicated severe renal insufficiency. Her sudden death suggested circulatory failure; and this was the conclusion of the physician in charge. McJunkin, Tweedy and Breuhaus,[11] in their study of acute parathormone poisoning in rats, state: "The circulatory failure which characterizes fatal cases is secondary to the degenerative lesions in the myocardium." The myocardial lesions in the patient under discussion were shown, by postmortem studies, to be widespread and severe. However, Dr. W. D. Forbus, who studied the case very thoroughly, states in the autopsy protocol: "The injury to the heart muscle seems of itself not sufficient to have produced myocardial failure. We must fall back, therefore, upon the theory of a general, severe intoxication as an explanation of the patient's death."

Dr. Fuller Albright, in a personal communication, makes the following comment: "It is my belief that your patient died of parathyroid poisoning which is a complication of hyperparathyroidism which occurs when the blood calcium rises above a certain critical point. At this critical point the serum phosphorus, instead of being low, starts going up because phosphorus is no longer diffusible at very high levels of calcium. The thing which would have alarmed me about your case was not so much the high calcium as the absence of a low phosphorus."

The peculiar manner in which calcium is deposited in the kidney parenchyma, nephrocalcinosis, as revealed by Roentgen rays, presents a picture *which is probably pathognomonic of hyperparathyroidism.* Of 6 instances of parathyroid adenoma, which have come under our observation at Duke Hospital, 3 were initially suspected of having hyperparathyroidism from the Roentgen ray appearance of the kidneys alone (Figs. 1, 6 and 7). The calcium deposit forms delicate, rosette-like shadows which we have never seen in any other condition.[5,6]

The only case reported in the literature that resembles the one just detailed was published in 1923 by Dawson and Struthers.[4]

The patient, a man of 49, on lifting a heavy weight, felt a sudden pain in his left upper arm, which gave way with an audible crack. Roentgen ray pictures showed a fracture. Four months later Roentgen ray pictures were made of the bones and fibrocystic disease with generalized decalcification was noted. Eight months from the time he was first seen, he was suddenly seized with a heart attack and was admitted in the evening in a state of collapse with a very rapid and feeble pulse. He was too ill to give an account of himself and died suddenly the following morning. No determination of the serum calcium and phosphorus was made.

Postmortem examination showed generalized osteitis fibrosa cystica, and at the left lower pole of the thyroid gland an ovoid tumor 1 inch in length was found. The authors were totally unable to connect the parathyroid tumor with the bone changes. Calcification was found in the form of fine granules in all the internal organs and in all the tissues of the body, especially in the elastic fibers and fine connective tissue fibrids. The pathologic findings as reported by Dawson and Struthers resemble very closely, with the exception of the fibrocystic bone changes, the findings in the case reported in this paper.

Lowenburg and Ginsburg[9] have reported the condition produced in a boy of 5 who was given 100 units of parathyroid extract daily for 6 days by mistake, 20 units having been ordered. The child became listless, drowsy, febrile and vomited now and then. The calcium rose to 19.6 mg. %. Recovery quickly ensued, with a return of the serum calcium to normal, when the parathormone was discontinued.

One point of great interest in the report of this accidental experiment is the occurrence of a considerable degree of fever as a result of parathormone poisoning. When surgeons were called in consultation to see the patient who forms the subject of the present paper, they found the temperature elevated to 38.5° C., and advised that operation be postponed. No one who studied the patient properly evaluated the grave danger indicated by the extremely high and increasing calcium level in the blood. Two days after admission the blood calcium was found to be 20 mg. %, and 3 days later it was 22 mg. %. Between the two tests the patient was examined by several observers. It is a logical inference that the inevitable palpation of what proved to be a large parathyroid adenoma resulted in more parathormone being expressed into the blood than otherwise would have occurred, with consequent increase of the hypercalcemia and toxemia. It is well known that mild manipulation of chromaffin tumors frequently precipitates attacks of paroxysmal hypertension.[7]

The calcification associated with hyperparathyroidism has been explained as a precipitation into relatively alkaline tissues of the calcium with which the plasma is supersaturated, that is, as a true

"metastatic" calcification. It is impossible to deny that this may occur, but tissue necrosis unquestionably precedes the deposit of calcium in hyperparathyroidism. Such necrosis was obvious throughout the organs in the case here reported. McJunkin, Tweedy and Breuhaus,[11] working with rats, and Cantarow, Stewart and Housel,[2] using dogs, have clearly shown that acute parathormone poisoning causes local degenerations of tissues, which are primary, and precede calcification. In their experiments such necroses were constant and widespread in the myocardium and kidneys, the great majority of regressive lesions showing no deposition of calcium, indicating that degenerative changes preceded calcium deposition.

All writers agree that parathormone in large doses is very toxic for dogs, rapidly producing weakness, anorexia, vomiting, gastrointestinal hemorrhage, respiratory distress, evidences of general circulatory failure and acute renal failure. Such animals show a hypercalcemia, nitrogen retention, dehydration, increased coagulability of the blood, and all the evidence in the urine of acute kidney damage. These are manifestations of parathormone poisoning produced rapidly by large amounts of the hormone, and, although enlightening, yet are not strictly comparable to the chronic form of parathormone intoxication, with terminal acute poisoning, as exhibited by the case herein reported. That the body can habituate itself to large amounts of parathormone was pointed out by Collip,[3b] and has been amply proven in the treatment of surgically produced hypoparathyroidism,[10] where the hormone may lose its effectiveness after a relatively short time. There is some evidence that a sufficient supply of vitamin D prevents the development of this tolerance to parathormone.[10]

From the clinical standpoint it is important to realize that 20 mg. % of calcium in the blood is indicative of a very critical condition. Recovery is possible if the parathyroid tumor is removed, even where the hypercalcemia reaches 22 mg. % or slightly higher. Shapper[13] has reported one reading of 23.6 mg. %, with eventual recovery; but it is obvious from experiments on dogs and from the case here reported, that a hypercalcemia approaching 20 mg. % is evidence of a dangerous degree of parathormone poisoning. Fuller Albright advises that patients with hyperparathyroidism be placed on a low calcium diet, especially when the phosphorus tends to be high.

Conclusions. An instance of hyperparathyroidism with fatal parathormone intoxication is reported, thus filling an existing gap in the natural history of the disease.

A characteristic type of parenchymatous renal calcification is illustrated, which is believed to be pathognomonic of hyperparathyroidism.

A blood calcium level approaching 20 mg. % is indicative of severe and dangerous parathormone intoxication.

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NOTES ON CHEMICAL STUDIES OF A GAUCHER SPLEEN.

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The presence of cerebrosides in the spleens of patients suffering from Gaucher's disease has been demonstrated by many investigators. Although the cerebroside present is normally supposed to be kerasin, Lieb and Mladenonic[8] were able to show the presence of a small amount of phrenosin in addition to kerasin in the spleen of a 5½-month-old child with Gaucher's disease. Capper, Epstein, and Schless[2] also have reported the presence of phrenosin in addition to kerasin in the spleen of a child, 6 years of age, with this disease. However, they gave no details as to the method of identification.

In 1935 Horsley, Baker and Apperly[5] reported a case of Gaucher's disease in a man 47 years old at the time of his death. The spleen removed at autopsy weighed 5890 gm. The results of a preliminary chemical analysis of a small portion of this spleen were reported at that time; but it was felt that a further analysis of the material to prove the presence or absence of phrenosin would be justified. Accordingly, a part of the spleen which had been fixed in formaldehyde was cut into small pieces, thoroughly washed with water, ground in a meat chopper and dried. The total ether and alcohol extractives were first determined and are given in Table 1 along with results obtained by other investigators.

Procedure for Cerebroside Isolation. The finely ground and dry splenic powder was first extracted repeatedly with cold acetone and

* Presented by one of us (J. S. McC.) in partial fulfillment of the requirements for the degree of Master of Science.

then with ether. The residue, which contained the cerebroside, was extracted twice with boiling 96% alcohol and filtered hot. On cooling to room temperature a white granular substance separated out. This was filtered off and the filtrate used several times to re-extract the splenic powder. The final filtrates were concentrated to about half their original volume and cooled to 0° C. A white creamy material separated out which was filtered off and combined with the previously isolated cerebroside. Further concentration and cooling gave no additional precipitation.

TABLE 1.—ETHER AND ALCOHOL EXTRACTIVES IN GAUCHER SPLEENS.

Author.	Age of patient.	Percentage of extractives. Ether soluble.	Alcohol soluble.
Epstein[4]	35 yrs.	6.7	34.95*
McConnell, Forbes and Apperly (present authors)	47 yrs.	7.0	30.4†
Bloom and Kern[1]	..	7.5	22.4
Lieb[7]	3 yrs.	6.75	11.85
Lieb and Mladenonic[8]	3½ mos.	5.2	9.3

* Calculated on the dry weight of the extracted material.

† This is the average of a number of determinations. It is slightly higher than the results obtained on a small sample of this spleen and reported in a previous paper.[5]

In attempting to purify the crude cerebroside by recrystallization from alcohol, two fractions were obtained. One fraction precipitated readily at 37° C. while the other was soluble at this temperature but separated out when the solution was cooled to 0° C. This separation into two fractions was not dependent upon the concentration of the solution, for when the 37° C. fraction was recrystallized and the filtrate concentrated and cooled to 0° C. very little material precipitated out. Similarly when the 0° C. fraction was recrystallized no precipitate was obtained at 37° C.

The fraction separating out at 37° C. was recrystallized several times from alcohol and acetone without any apparent improvement in the appearance of the product. Consequently, Klenk's[6] method for the purification of cerebrosides was resorted to. The final product obtained was pure white and when heated showed a clearing point of 178° C. which was not changed by further recrystallization. Examination of the material with a selenite plate (gippsplate) as described by Rosenheim[9a] showed the typical refractive picture of kerasin. Another sample of the crude cerebroside was purified by Rosenheim's[9a] method and an identical product was obtained. After acid hydrolysis, sphingosine sulphate, galactose and a fatty acid which melted at 80.4° C. were obtained. This melting point agrees with that usually given for lignoceric acid, 80 to 81° C. as opposed to 101.5 to 103° C. for cerebronic acid. Attempts at acetylation were uniformly unsuccessful furnishing further proof of the absence of cerebronic acid and thus of phrenosin.

Elementary analysis of the purified cerebroside with values reported by a few other investigators for kerasin are given in Table 2.

TABLE 2.—ELEMENTARY ANALYSIS OF THE PURIFIED CEREBROSIDE.

Author.	Carbon, %.	Hydrogen, %.	Nitrogen, %.
Lieb and Mladenonic[8]	69.76	11.24	
Lieb[7]	70.74	11.35	1.98
Rosenheim[9b]	68.94	11.40	1.80
McConnell, Forbes and Apperly (present authors)	70.60	11.23	1.73

The alcohol soluble material which precipitated only when the solution was cooled to 0° C. was purified by Rosenheim's[9a] method and found by clearing point and the selenite plate test to be kerasin. We have no explanation for the difference in solubility of the two kerasin fractions. However, it might be due to differences in the fatty acid part of the molecule since Chibnall *et al.*[3] have shown that lignoceric acid is not a true chemical substance but a mixture of several fatty acids.

Conclusions. The cerebroside in the spleen of a middle aged man who died from Gaucher's disease has been isolated and found to be kerasin. Phrenosin was absent.

We wish to thank Dr. Paul Kimmelstiel for his many helpful suggestions during the course of this investigation.

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A CASE OF HODGKIN'S DISEASE WITH MASSIVE COLLAPSE AND CAVITATION OF THE LUNG.

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WHEN intrathoracic Hodgkin's disease is mentioned, one usually thinks of enlarged mediastinal glands that may give rise to pressure signs like cough and venous engorgement and eventually grow out of the mediastinum into the parenchyma of one or both lungs. One does not usually think of Hodgkin's disease as being able to cause such pulmonary complications as pleurisy,[11] hydrothorax,[15] pneumothorax,[4, 9] cavitation, bronchiectasis,[14] and atelectasis. Nor does one

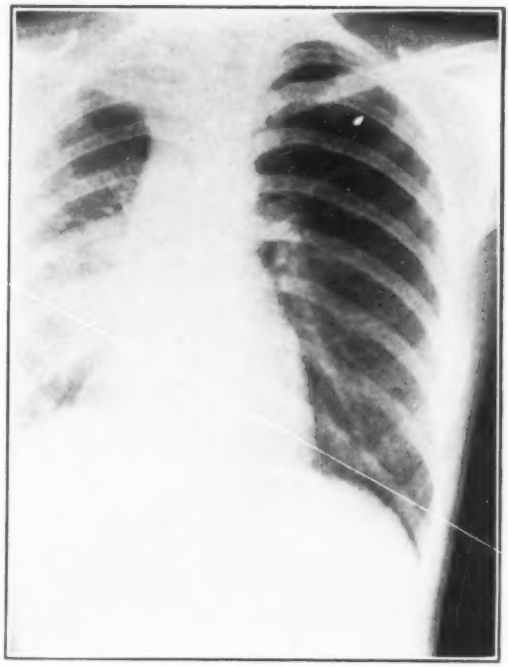

FIG. 1.—December, 1934. Partial atelectasis of right lung; small part of upper and large part of lower lobe.

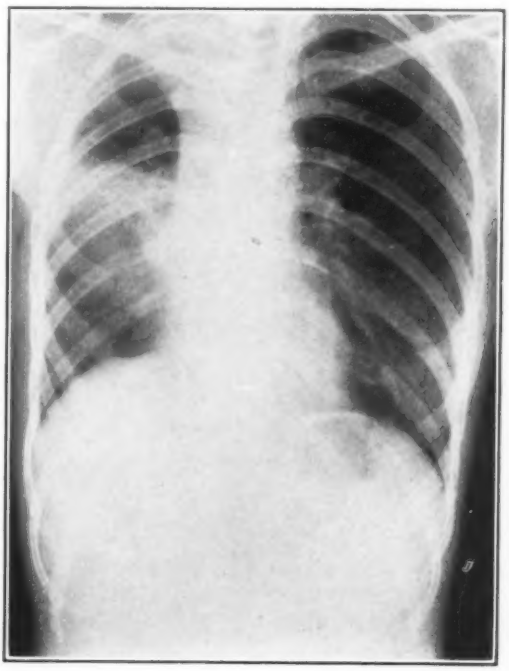

FIG. 2.—May, 1935. After Roentgen-ray therapy to right chest.

FIG. 3.—October, 1935. Massive collapse of right lung.

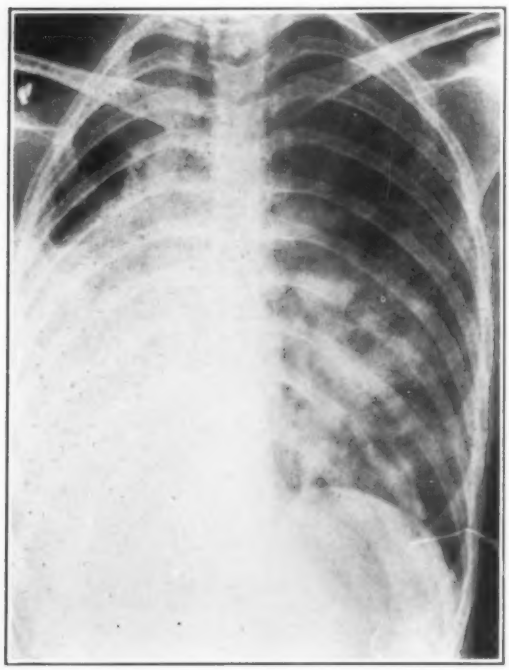

FIG. 4.—October, 1936. Large cavities of upper, atelectasis of lower right lung; infiltration of lower left lung.

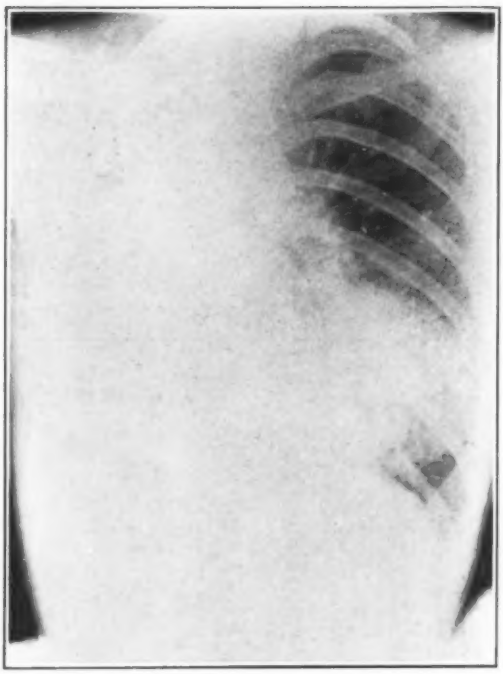

FIG. 5.—December, 1936. Massive collapse of right lung; great increase in consolidation of left lung.

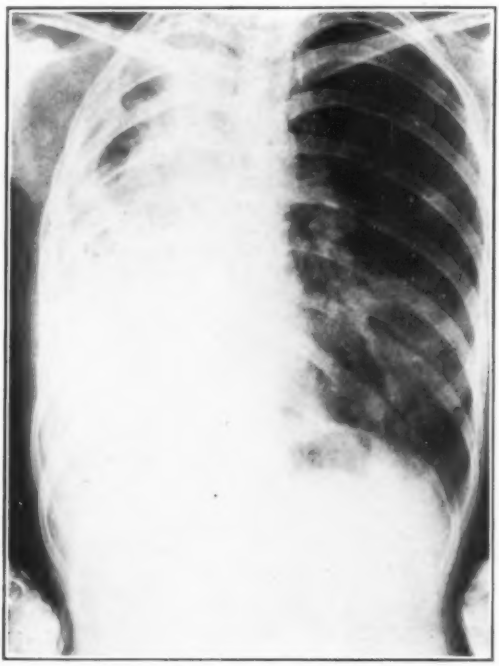

FIG. 6.—April, 1937. Large cavity and atelectasis on right; infiltration and multiple cavities on left.

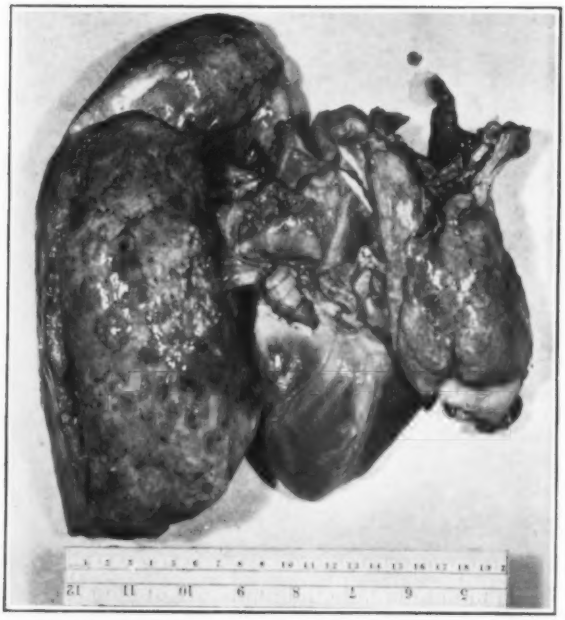

FIG. 7.—Small right lung solid with Hodgkin's granuloma except the upper portion which forms a large cavity. Infiltration of the wall and constriction of the lumen of the right main bronchus. Enlarged mediastinal glands. Dextrocardia. Large left lung studded with nodules of granuloma.

think of it as being able to produce a picture like metastatic carcinoma or miliary tuberculosis of the lung.

It would seem natural to suppose that partial or complete atelectasis due to pressure upon and occlusion of a bronchus by an enlarged mass of mediastinal or bronchial glands would be a fairly common complication of mediastinal Hodgkin's disease, especially since compression of the superior vena cava and trachea occurs so often. But this is not the case. Partial atelectasis occurs infrequently, and I can find but 2 reported cases of massive atelectasis. Both of these were complicated by pleural effusion. In every one of these cases of partial or complete atelectasis that came to autopsy the bronchial obstruction was due not to the pressure of enlarged glands upon the bronchial wall, but to the invasion of the bronchial wall by Hodgkin's tissue, granulomatous plaques being found in the bronchial submucosa and mucosa. In other words, the obstruction was inside, not outside, the bronchus.

History of Atelectasis of the Lung in Hodgkin's Disease. Although Hurd[6] in 1922 discovered by bronchoscopy a partial constriction of the left bronchus, due apparently to the enlarged mediastinal glands of Hodgkin's disease in a woman who had cough and impaired aeration of the lung bases, real lobar atelectasis was not reported until Junghagen[8] in 1926, Wachner[17] in 1934, and Loeper and Bioy[10] in 1935, each presented a case of atelectasis of the right upper lobe of the lung due to Hodgkin's disease. Atelectasis partially cleared in one and completely cleared in another following radio-therapy. Wachner's case, the only one autopsied, showed narrowing of the right upper lobe bronchus due to infiltration of its wall by Hodgkin's granuloma.

In 1932 Paviot, Levrat and Jarricot[13] reported the first case of massive collapse of the lung due to Hodgkin's disease. It was the case of a woman of 22 with Hodgkin's disease of about 4 years' duration. She first had axillary glands; these were followed by general glandular enlargement, cough, fever, pains in chest, a right and then a left pleural effusion. There was only temporary improvement after Roentgen ray treatment over the mediastinal glands and several left thoracenteses. Just before death the dyspnea was violent, expiratory, prolonged and wheezing. At autopsy, there was found an enormous glandular mass encircling the left bronchus up to the level of tracheal bifurcation. The lining of the left bronchus was invaded and the lumen obliterated by the granuloma. The left lung was atelectatic, the atelectasis being the result both of bronchial obstruction and pleural effusion.

Moolten[12] in 1934 reported the second case of massive collapse of the lung due to Hodgkin's disease. A man of 49 had a gland in the left parotid region for 18 months, followed by fever and a cough productive of blood-streaked sputum, and rather severe dyspnea with acute attacks of wheezing. Physical examination gave signs of a massive right pleural effusion. Roentgen ray showed, in addi-

tion, a paradoxical shift of mediastinal structures towards the right. The patient being too ill for bronchoscopy, thoracotomy was done, and when the fluid was removed the lung was seen to be collapsed. An attempt to reëxpand the lung by forced air pressure intratracheally failed. At autopsy, a polyp composed of Hodgkin's granuloma was found inside the orifice of the right main bronchus completely obstructing it. This is the first case report of massive collapse of the lung due to an endobronchial polypoid tumor composed of Hodgkin's granuloma. Moolten described another case in which partial occlusion of both main bronchi was found at autopsy. A bilateral pleural effusion probably prevented the clinical diagnosis of atelectasis. The bronchial and tracheal submucosa were infiltrated with granuloma so that the orifices of both main bronchi were narrowed and markedly obstructed.

Weber[18] in 1930 and Versé[16] in his monograph in 1931 discuss the pathology of bronchial occlusion and atelectasis in Hodgkin's disease of the lung. Both describe involvement of the bronchial mucous membrane with Hodgkin's granuloma.

Case Report. Miss G. H., 22-year-old unmarried Jewess, was first seen December 3, 1934, complaining of cough for 2 years. Family and past history non-contributory. Cough with production of a profuse, sometimes blood-streaked, odorless sputum began about 2 years ago; worse in early morning and late evening. Fever on and off for 2 years. Small swelling above right clavicle noted 2 months after cough began; it has increased and decreased in size but never disappeared. Profuse night sweats during last year. There was pain in right upper and lower chest with temperature 103° F. a year ago, at which time a diagnosis of pleurisy was made and a physician obtained a small amount of clear fluid from a thoracentesis. Six sputum examinations negative for tuberculosis. Roentgen ray of chest in March, 1933, showed dense shadow at right apex; October, 1933, dense shadow right base; March, 1934, dense shadow right apex. Basal metabolism in March, 1934, normal. Present weight 103, no gain and no loss. Pain in front of upper right chest for past 3 nights.

Physical Examination: T. 99.6° F.; P. 100; B.P. 117/70; Wt. 103 pounds. Well developed and nourished thin girl with a good color. Eyes, ears and nose normal. Teeth poor condition; dental caries, pyorrhea, gold crowns, bridgework. Throat negative. Tonsils removed. A node almost the size of a walnut palpable just above right clavicle and lateral to sterno-cleido-mastoid muscle; movable, not tender, not fixed to the skin. No other glands enlarged anywhere. Left lobe thyroid palpable but not enlarged. Heart: PMI felt just inside mammary line. Dullness to percussion to right of sternum in fourth and fifth interspaces extending from just medial to right midclavicular line to sternum. Heart sounds good quality, no murmurs, rhythm normal, rate rapid. Right chest: some atrophy of trapezius; motion of chest limited; tactile fremitus decreased; percussion note everywhere dull except at base where it was flat; faint breath sounds at apex, absent breath sounds elsewhere; no bronchophony or pectoriloquy. After a paroxysm of coughing bubbling and sibilant râles were heard. Left chest: hyperresonant; breath sounds normal but loud. Abdomen: negative; liver and spleen not palpable. Extremities negative. Reflexes active. A tentative diagnosis was massive collapse of the right lung. Roentgen ray of lungs* (Fig. 1) showed no active disease of left lung but an extensive

* All Roentgen ray interpretations and treatments were by Drs. A. B. Moore and E. M. McPeak, Roentgenologists at Emergency Hospital.

inflammatory process involving lower three-fourths of the right lung, multiple areas of bronchiectasis, and a central area at level of eighth rib posteriorly which appeared to be a necrosing pneumonitis, a thickened pleura in the region of the right hilus and a partial atelectasis of the right lung.

TABLE 1.—BLOOD FINDINGS.

Date.	Hgb. % (Sahli).	R.B.C. mill. per c.mm.	W.B.C. thous. per c.mm.	Differential. P.	L.	M.	E.
12/ 5/34	75	3.9	11.6	56	44		
1/10/35	90	5.4	17 5	73	25	..	2
4/ 4/35	80	5.7	12.3	77	20	..	3
5/ 9/35	75	3.7	15.6	78	18	2	2
9/25/35	70	4.5	16.5				
4/13/36	70	3.8	18.3	92	8		
10/22/36	72	3.7	10.1	79	9	10	2
4/10/37	72	4.8	15.7	96	4		
4/17/37	Blood culture—72-hour cultures sterile						

December 10, 1934. In order to determine, if possible, the cause of the atelectasis, bronchoscopy was performed by Dr. D. B. Moffett. "Considerable inflammation of the right main bronchus which is increased where it divides. Thick, heavy, mucus-like pus in entire region, resembling bronchiectatic exudate, more being obtained from bronchus to lower lobe than elsewhere." Two attempts at lipiodol Roentgen films were unsuccessful because the patient coughed up all the lipiodol. However, the picture showed improved aëration of the right lung following bronchoscopy.

January to April, 1935. With the idea that we were dealing with a bronchiectatic infection or an abscess, an artificial pneumothorax in the right chest was accomplished by Dr. W. D. Tewksbury. The physical signs changed to those of a typical right-sided pneumothorax. There was some improvement in the patient's clinical condition at first but cough persisted, a chain of new glands appeared in the right neck, and there was 6 pounds loss of weight. A biopsy of a cervical gland (April 27) was reported upon as follows (Dr. J. W. Lindsay): "On section the gland is hard and gristly. The cut surface is apparently largely fibrous tissue. Microscopic section shows dense fibrosis with irregular islands of lymphoid elements. The follicular structure has been destroyed and there are great numbers of eosinophilic and single and multinucleated giant cells, the latter typical Sternberg-Reed type. Diagnosis: Hodgkin's Disease." We had not thought of Hodgkin's disease before this report.

May to September, 1935. There was an aggravation of the atelectasis after the pneumothorax air was absorbed. Following Roentgen-ray therapy to the right chest and neck there was great improvement in signs and symptoms, but Roentgen ray (Fig. 2) May 15 showed still some infiltration in middle third of right lung. There were resonance, fremitus, and bronchovesicular breathing at right upper lobe, dullness and absent breath sounds right lower chest, and disappearance of enlarged glands. In a week aëration of right upper lobe had disappeared. After further radiotherapy to right chest (June) there was an increase in density of upper right lobe with the appearance of multiple small cavities. During the summer the patient had pain in back of neck extending down to shoulders and arms, fairly constant afternoon fever, though there was one afebrile period lasting a week, cough with thick yellow profuse sputum daily with paroxysms morning and evening.

October, 1935, to May, 1936. Following another course of radiotherapy to the right chest (September and October) there was a great aggravation of symptoms. Roentgen ray (Fig. 3) October 23 showed complete atelectasis on right side with heart and mediastinum drawn completely to this

side. The patient walked into my office and showed the following signs: T. 104° F.; P. 166; R. rapid; B. P. 90/70; Wt. 90 pounds. No enlarged glands. Trachea to right. Right upper chest sunken in. PMI 4 cm. from MCL in 5th i.s. Heart racing, gallop rhythm, sounds as well heard to right as to left of sternum, no murmurs. Right lung: flat everywhere except for slight resonance over upper lobe behind and between scapula and vertebræ where breath sounds were tubular. Elsewhere breath sounds either very faint or absent. Left lung clear. Abdomen negative. She was sent home to bed immediately. (There was no further radiotherapy to the chest but several treatments to the cervical glands periodically. The glands always responded well to treatment.) She was ill at home during November and December. The cardiac p.m.i. was found in 3rd i.s. in right mammary line, there being no cardiac dullness in the left chest. Physical signs otherwise remained the same. Cough, sputum, and fever were constant.

June to December, 1936. By June 2 cavities had appeared in right apex and there was a beginning infiltration at left hilus. Roentgen ray (Fig. 4) October 9 showed some decrease in consolidation of right lung with large cavities and a more marked involvement at left base. Amphoric breathing at apex. Roentgen ray (Fig. 5) December 9 showed complete consolidation on right with a great increase in consolidation at left base. Physical signs were: cardiac p.m.i. in 2d, 3d and 4th i.s. on right side in M.C.L.; gallop rhythm. Dullness and faint amphoric breathing over right lung, an increased expiratory phase in left axilla.

January to May, 1937. Dyspneic, glands, T. 98.8° F. to 102° F.; P. around 130; R. around 30; B. P. 110/80; Wt. 87 pounds. In bed most of time. Râles at base of left lung followed later by prolonged and grating expiration, expiratory sonorous râles and dullness. The right lung was dull, with tubular breathing at apex and absent breath sounds elsewhere. Clubbing of fingers. On April 9 a severe dyspnea brought on by coughing. Respiratory wheezes very loud. Pulse 150, respiration 46. Ambulance to Emergency Hospital where she stayed until April 25. In an oxygen tent for most of hospital stay. The oxygen immediately cleared up the dyspnea. Physical signs about the same except that there was amphoric breathing over most of right lung and loud wheezing over the left. Morphine used for the first time. Afebrile for last 6 days. A portable Roentgen ray (Fig. 6) April 10 showed atelectasis on the right with practically complete destruction of lung tissue, and multiple cavities on the left with no definite consolidation noted. After her return home glucose intravenously cleared up an attack of vomiting on April 30. On May 24 there was difficult respiration and twitching of the extremities, followed by coma and an uncountable tachycardia. No response to adrenalin. The heart stopped a minute after the respiration.

Two urine examinations (December 5, 1934 and April, 12, 1937) were essentially negative. Sputum negative for acid-fast bacilli (December 16, 1936), cultures positive for non-hemolytic streptococci, *Strep. viridans* and *S. albus*. Positive for monilia albicans (January 13, 1937). (See Table 1 for blood findings.)

Autopsy (Dr. E. C. Rice). Body is that of an emaciated white female, apparent age 30 years, estimated weight 90 pounds. The muscular development of the right chest seems less marked than the left. A mass of enlarged lymph nodes can be palpated in the right anterior axillary line. *Thorax:* On reflecting the pectoral muscles the hyperplastic lymph nodes are found to be much enlarged and have a grayish homogeneous appearance, averaging 1.5 cm. in diameter. *Thymus:* rudimentary. *Mediastinal and Bronchial Lymph Nodes:* Are markedly enlarged, relatively firm and of a grayish-white homogeneous appearance. The mediastinal form an irregular mass measuring roughly 5 by 3 by 2 cm. The bronchials are likewise

enlarged and are intimately associated with the infiltrating new growth involving the lungs. *Pleural Cavities:* The right has been obliterated by the extensive change involving the corresponding lung. Light adhesions bind the lower lobe of the left lung to the adjacent lobe and the parietal pleura. *Lungs—right* (Fig. 7): Only a small portion of the lung remains, being densely bound to the parietal pleura and a mass of enlarged lymph nodes at the apex. A cavity filled with green pus is found involving the greater portion of the upper and middle (?) lobes, very little lung tissue remaining. The lower lobe is represented by a firm mass about the size of an adult male fist. On section, it is made up of a cartilaginous like mass of gray tissue which has infiltrated and practically destroyed this lobe. The right bronchus is narrowed 2 cm. below the bifurcation of the trachea to a diameter of 3 mm. due apparently to an infiltration of the wall at this point. The tube below contains grayish-green purulent material. The *left lung* (Fig. 7) shows compensatory hypertrophy. Its surface is a light grayish-pink. A number of firm areas can be felt throughout the upper lobe, which is air containing. The lower lobe is firm with some tissue along the lower border showing less density. On section, the upper lobe is infiltrated by a number of gray nodules, averaging 5 to 10 mm. in diameter, mostly in the lower portion. The lower lobe has a mosaic-like appearance due to massive infiltration of grayish homogeneous fairly firm masses. These vary in diameter from a few mm. to 3 cm. Very little lung tissue remains. Numerous cavities are present, filled with greenish-gray purulent material. The largest measures 4 cm. in diameter and is adjacent to the hilum. The bronchi contain thick gray muco-purulent material. *Pericardial Sac:* Drawn to the right by adhesions. The fluid is of normal amount, no cardiac adhesions being noted. *Heart*: Is of normal size, being situated largely in the right thoracic cavity. The epicardium contains a number of rather firm yellow areas along the coronary vessels and near the base of the heart. The myocardium is flabby and pale. The mitral ring is thickened. ABDOMEN: *Peritoneal Cavity:* No fluid or adhesions. *Liver:* moderately enlarged, fatty and passively congested. *Spleen:* moderately enlarged, fairly soft. Beneath the capsule are a number of grayish-yellow areas, approximately 5 mm. in diameter. The pulp is relatively firm and deep reddish-brown. *Adrenals:* enlarged, firm, congested medulla. *Kidneys:* normal size; left capsule strips with resistance, roughened; they section with increased resistance, the cortical and medullary portions not being well differentiated, the tissue dull reddish-brown color; there is probably some cloudy swelling and fibrosis. *Retroperitoneal lymph nodes:* a mass 3 cm. in diameter found at level of left renal vein. *Gall bladder, pancreas, g. i. tract, bladder and generative organs:* normal.

Anatomical Diagnosis: 1. Generalized lymphadenopathy with metastasis to lungs, bronchus and spleen (Hodgkin's disease). 2. Pleural adhesions, bilateral. 3. Cavitation of lung, right. 4. Hypertrophy of lung, left. 5. Chronic bronchitis. 6. Dextrocardia. 7. Subacute or chronic nephritis. 8. Malnutrition.

MICROSCOPIC (Dr. J. W. Lindsay): *Bronchus*: Marked increase in connective tissue throughout the wall. The mucosa is somewhat hyperplastic but uniform. Throughout the section and particularly in the mucosa, dense infiltration by round cells and a few neutrophils. Eosinophils are not common nor are giant cells seen. Diagnosis: Chronic bronchitis (Hodgkin's disease?). *Lung:* Only occasionally can an alveolar pattern be recognized, the architecture being largely replaced by dense fibrous tissue which is extensively infiltrated by round cells, a few neutrophils but many eosinophiles. Giant cells of the Reed-Sternberg type are common. A few areas of necrosis are noted. Diagnosis: Hodgkin's disease. *Heart:* Marked edema, sparse infiltration by round cells and considerable degeneration. *Spleen:* Diffuse and marked fibrosis with considerable loss of architecture,

Dense infiltration by leukocytes (round cells, neutrophils, eosinophiles) and scattered areas of degeneration. *Liver:* Marked fatty change and irregular round cell infiltration in the portal spaces. *Adrenal:* Parenchymatous degeneration and moderate edema. *Kidney:* Marked edema, considerable parenchymatous degeneration and sparse round cell infiltration. *Pancreas:* Marked edema. *Lymph node:* The follicular pattern is often almost completely disrupted by extensive fibrosis, round-cell and eosinophilic infiltration. Numerous Reed-Sternberg giant cells are noted, the picture being quite characteristic of Hodgkin's disease.

Discussion. There are several interesting points in this case worthy of discussion.

Diagnosis. The difficulty arose from not thinking of Hodgkin's disease as a possibility and attention being focussed on the lung to the exclusion of the supraclavicular lymph gland.

Mechanism of Atelectasis. The variability of the atelectasis was striking. Within 5 or 6 months (history) the atelectatic right upper lobe became normal and the right lower lobe became atelectatic, and *vice versa.* In other words, the mechanism that caused the obstruction was inconstant in its behavior. Following bronchoscopy, which gave no evidence of bronchial obstruction by enlarged glands, the atelectatic right lower lobe contained a small amount of air. Following a productive cough there were bubbling and sibilant râles over the collapsed lobe. In other words, when mucus was aspirated or coughed up the bronchial obstruction became incomplete. Finally there was neither Roentgen ray nor postmortem evidence of a great enlargement of mediastinal glands, the autopsy showing no bronchial obstruction from the enlarged glands that were present. It would seem, therefore, that the bronchial obstruction was not due to mediastinal glands but rather to a tenacious, mucopurulent exudate[7] arising from the severe bronchitis secondary to direct involvement of the bronchial tube with Hodgkin's disease. Constriction of the bronchial lumen was produced by a Hodgkin's infiltration into the bronchial wall, the bronchitic exudate changing constriction to obstruction. This explanation would account for the variability of the atelectasis, the slight aëration after bronchoscopic aspiration of mucus, and the occasional presence of râles over the affected lobe during a paroxysmal cough productive of large amounts of tenacious sputum. As time went on more and more of the parenchyma undoubtedly became infiltrated so that eventually the entire lung was solid with granuloma. With all bronchi, bronchioles and alveoli obliterated by granuloma the lung would be atelectatic even if its main bronchus were not obstructed.

Moolten[12] has recently discussed the bronchitis that is so typical of Hodgkin's disease of the lung and that had previously been described by Ziegler, Versé and others. It "may appear to the pathologist as a simple chronic or acute bronchitis. . . . Frequently, however, the specific nature of the bronchitis is suggested by plaque-like opacities in various parts of the mucosa or by elevated areas or bulky nodular outgrowths which narrow the lumen considerably."

Response to Roentgen Ray Therapy. There was some clearing of the atelectasis with great clinical improvement following the first Roentgen ray treatment to the affected lung. When this was repeated 4 months later the patient became very ill with a severe reaction, characterized by vomiting, high fever, and massive collapse of the lung. The lung had become resistant to Roentgen ray therapy. Radiation of the chest was not attempted again. On the other hand, response of the neck glands to radiotherapy was always satisfactory.

Cavitation of Lungs. This has been several times reported as a complication of Hodgkin's disease of the lung parenchyma.[1,18] Thought at first to be due to a necrosis from radiotherapy, it has since been described as occurring spontaneously.[17] In the case under discussion multiple small cavities were described by the rontgenologists immediately after the first intensive radiotherapy to the right chest in May and June, 1935. Two cavities in the right apex appeared a year later (Fig. 4), 8 months after the second and last course of radiotherapy to the chest when massive collapse was first noted. No doubt necrosis existed and cavitation was potential during the period of massive collapse. From these two examples it would have appeared that cavitation was caused by radiotherapy. On the other hand, multiple cavities eventually occurred in the left lung which at no time had been exposed to radiation (Fig. 6).

Fungus Infection. The finding of monilia albicans in a culture of the sputum probably has no pathologic significance in this case. The association of moniliasis[5] and of torulosis[2,3] with Hodgkin's disease has been reported.

Summary. The clinical course and autopsy findings of a young woman with Hodgkin's disease complicated by atelectasis and cavitation of the lung are given in some detail. Comparable cases reported in the literature are briefly summarized, and the mechanism of atelectasis and cavitation is discussed.

The author wishes to express his appreciation of the help given him in the study of this case by those already mentioned in the text (particularly by Drs. J. W. Lindsay, E. M. McPeak, A. B. Moore and E. C. Rice); by Drs. L. Hamman, W. T. Longcope and W. G. MacCallum, of Baltimore; and by Miss Anne Hill, his secretary.

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VENOUS BLOOD PRESSURE MEASUREMENTS DURING SYNCOPE CAUSED BY A HYPERIRRITABLE CAROTID SINUS REFLEX.

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Syncope caused in some individuals by the hyperactive carotid sinus reflex has been receiving deserved emphasis lately.[1,3–5] While much information concerning this important reflex continues to accumulate, many of its aspects still intrigue investigators. This report embraces the venous blood pressure findings before, during and after the syncope induced by carotid sinus pressure.

With an abnormally sensitive carotid sinus—the bulbous dilatation at the bifurcation of the common carotid artery—an increase in intrasinus pressure often causes syncope, with or without cardiovascular changes. Weiss and his colleagues[5] have ably classified the types of sinus response. These are: 1, the vagal type, characterized by sino-auricular or auriculo-ventricular block with its resultant asystole and syncope; 2, the depressor type characterized by marked drop in blood pressure unassociated with arrhythmia; and, 3, the cerebral type, in which syncope occurs without changes in the cardiovascular system or total blood flow through the brain.

In 8 such cases we have had the opportunity of determining the venous blood pressure during induced carotid sinus syncope.

Under basal conditions, with the normal individual in a recumbent position for at least 15 minutes, the normal venous pressure registers between 4 and 6 cm. of water, while the upper normal limit does not exceed 11 cm.[2]

Method. We employed the usual sterile apparatus for determining venous blood pressure, consisting of an 18-gauge needle connected by rubber tubing to the short right-angled arm of a water manometer graduated in millimeters and filled with sterile physiologic saline. Although ordinarily, when venous pressure is determined, the patient lies recumbent, with the arm on a level with the right auricle, our patients were tested while standing.

This change was necessary (except in 1 case) because the horizontal position frequently abolishes the syncope and other effects of a hyperirritable carotid sinus reflex. One of the patient's arms was held horizontally outstretched by an assistant, on as nearly a level with the right auricle as possible. The needle was inserted into the vein. The saline filled manometer was then attached. The height of the saline column, indicating the venous pressure was recorded. On the other arm a sphygmomanometer registered the arterial blood pressure. Then digital pressure was made over that portion of the carotid artery from the cricoid cartilage to the angle of the jaw. The patient was supported by a second assistant to prevent falling and displacing of the apparatus. Venous and arterial blood pressure readings were made throughout.

Our clinical material comprised 8 patients with a hyperirritable carotid sinus reflex. There were no anomalous differences in the arterial or venous blood pressures in either arm.

A brief summary of the data in each case follows:

CASE 1.—*Vagal and Depressor Sinus Response.* A. B., male, aged 24. Initial standing pulse 70, arterial blood pressure 120/80 (left arm), venous blood pressure 12 cm. water (right arm). Right carotid sinus pressure maintained for 10 seconds caused a decrease in the pulse from 70 to 22, a fall in arterial blood pressure from 120/80 to 80/60 and a generalized clonic convulsion and syncope lasting 6 seconds.

The venous blood pressure was unchanged until the convulsion when it rose from 12 cm. to 14 cm. It returned to its original level as soon as the convulsion ceased.

As in this patient carotid sinus pressure would invoke syncope even were he horizontal, the experiment was repeated in this position.

With the patient horizontal the initial pulse was 68, the arterial blood pressure 110/70, and the venous blood pressure 8 cm. water.

Right carotid sinus pressure caused a decrease in the pulse from 68 to 30, a fall in arterial blood pressure from 110/70 to 95/65 and a generalized clonic convulsion.

The venous blood pressure was unchanged until the convulsion when it rose from 8 cm. to 11 cm. It returned to its original level as soon as the convulsion ceased.

CASE 2.—*Vagal and Depressor Sinus Response.* J. C., male, aged 70. Initial standing pulse 80, arterial blood pressure 130/80, venous blood pressure 9 cm. water.

Pressure over either carotid sinus caused a decrease in the pulse from 80 to 60, a fall in arterial blood pressure from 130/80 to 80/60, and a generalized clonic convulsion and syncope.

The venous blood pressure was unchanged until the patient was actually convulsing when it rose from 9 cm. to 12 cm. It returned to its original level as soon as the convulsion ceased.

CASE 3.—*Vagal and Depressor Sinus Response.* A. Br., male, aged 57. Initial standing pulse 84, arterial blood pressure 108/80, venous blood pressure 10 cm. water.

Right carotid sinus pressure caused hyperpnea, disappearance of the pulse, a fall in arterial blood pressure from 108/80 to 60/? and a generalized convulsion and syncope.

The venous blood pressure was unchanged until the onset of hyperpnea when it rose from 10 cm. to 12 cm. and during the convulsion it rose to 13 cm. It returned to its original level as soon as the convulsion ceased.

CASE 4.—*Vagal, Depressor and Cerebral Sinus Response.* W. C., male, aged 57.

Initial standing pulse 76, arterial blood pressure 90/60, venous blood pressure 15 cm. of water.

Carotid sinus pressure caused a drop in blood pressure from 90/60 to 20/?, and a decrease of the pulse from 76 to 0, clonus of the mandibular muscles, and slumping to the floor.

The venous blood pressure was unchanged.

CASE 5.—*Vagal, Depressor and Cerebral Sinus Response.* J. Co., male, aged 14 years. Initial standing pulse 78, arterial blood pressure 108/70, venous blood pressure 12 cm. water.

Right carotid sinus pressure caused a decrease in the pulse from 78 to 65, a fall in arterial blood pressure from 108/70 to 60/40 and clonus of the contralateral limbs (left arm and leg).

The venous blood pressure was unchanged until clonus developed when it rose from 12 cm. to 13 cm. It returned to its original level as soon as the clonus ceased.

CASE 6.—*Vagal, Depressor and Cerebral Sinus Response.* W. P. G., male, aged 69. Initial standing pulse 68, arterial blood pressure 140/80 (right arm), venous blood pressure 7 cm. (left arm).

Pressure over either carotid sinus for 10 seconds caused a decrease in the pulse from 68 to 30, a fall in arterial blood pressure from 140/80 to 60/20, and clonus of the contralateral arm and syncope.

The venous blood pressure was unchanged throughout, registering at 7 cm. even during the actual clonus and syncope.

CASE 7.—*Vagal and Depressor Sinus Response.* L. S., male, aged 79. Mitral stenosis and insufficiency.

Initial standing pulse 70, arterial blood pressure 120/70, venous blood pressure 17 cm.

Pressure over either carotid sinus caused a decrease in the pulse from 70 to 40 and then disappearance of the pulse, a fall in arterial blood pressure from 120/70 to 80/60, and then to zero. Blurred vision, pallor and faintness supervened.

The venous blood pressure was unchanged until the pulse and arterial tension disappeared, when the venous pressure fell from 17 cm. to 15 cm. It returned to its original level as soon as the pulse and arterial tension returned on the release of carotid sinus pressure.

CASE 8.—*Cerebral Sinus Response.* M. S., female, aged 19 years. Initial standing pulse 84, arterial blood pressure 118/74, venous blood pressure 9 cm.

Pressure over either carotid sinus for 10 seconds caused a generalized clonic convulsion and syncope, unattended by any demonstrable change in the pulse or arterial blood pressure. The venous blood pressure was unchanged until the convulsion when it rose from 9 cm. to 11 cm. It returned to its original level as soon as the convulsion ceased.

The above results demonstrated that, prior to the convulsion, there was no significant change in venous blood pressure during the induction of carotid sinus syncope, even when the arterial blood pressure or cardiac rate fell. During the convulsion, the venous blood pressure tended to rise moderately, but promptly returned to its resting level as soon as the muscular activity ceased.

Summary. In 8 patients exhibiting a hyperactive carotid sinus reflex, measurements were made of the venous blood pressure before, during and after the induction of carotid sinus syncope.

There was no significant change in venous blood pressure, prior to the convulsion. During the convulsion the venous blood pressure tended to rise moderately, but promptly returned to its resting level as soon as the muscular activity ceased.

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PRESSOR EFFECT OF AMPHETAMINE ("BENZEDRINE") ON NORMAL, HYPOTENSIVE AND HYPERTENSIVE PATIENTS.

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One of the most interesting of the newer chemical compounds is amphetamine* ("Benzedrine"). Its use has been suggested in a wide range of clinical conditions.

Pharmacologic investigation has established it as a sympathomimetic amine having properties in many respects similar to those of ephedrine and epinephrine, to both of which it is closely related chemically.[6,7,14] Since such compounds usually exhibit a definite pressor effect, this characteristic must be considered by anyone using the drug therapeutically. It seemed desirable to note the effects of small doses of volatile benzedrine base, administered as a vapor, and also the effects of larger doses of the sulphate salt, given orally.

The preliminary procedure was the same in all subjects. After a complete rest period of from 10 to 15 minutes, a control blood pressure reading was taken. All readings were taken in the usual manner, using a standard sphygmomanometer with readings taken to the nearest multiple of 5. For the sake of brevity, diastolic pressures are not included in the tables, as they showed no significant variations. The pulse and, in many instances, the respiratory rate were taken simultaneously with the blood pressure.

A. Benzedrine Inhaler. Recently it has been shown that the usual dose of benzedrine obtained by inhalation from the inhaler is never more than 1 mg. in any single hour, or 5 mg. in any one day, and generally much less than these amounts.[17] Compared to the dosage necessary to obtain pressor effects by oral administration, it would seem that there should be no increase in blood pressure after its therapeutic use as an inhalant. There has been, however, an isolated case reported in which it was felt that the use of the inhaler might have caused an increase in blood pressure.[11]

In view of these facts, it seemed desirable to have more information on the effect of moderate acute overdosage with the Benzedrine Inhaler. Tests were made on 28 subjects. All were normals or ambulatory convalescent or recovered patients.

Twenty inhalations of benzedrine vapor from the inhaler were taken by the patient as quickly as possible. Blood pressure readings were taken at intervals of 5, 10, 15, 30 and 60 minutes. In a few instances, observations were continued beyond the usual 60-minute

* I am indebted to Smith, Kline & French Laboratories, who supplied the material used in this study.

period, but no noteworthy changes from the hour readings were detected. Results are shown in Table 1.

TABLE 1.—BENZEDRINE VAPOR IN NORMALS AND HYPERTENSIVES.

Patient.	Initial systolic.	Maximum variation mm. Hg in systolic pressure.	Patient.	Initial systolic.	Maximum variation mm. Hg in systolic pressure.
1	100	+10	15	165	+5
2	100	−10	16	165	−15
3	110	+5	17	170	+5
4	110	−5	18	175	−5
5	115	−5	19	180	+5
6	120	+5, −5	20	180	+10
7	125	−5	21	180	−5
8	130	+5, −5	22	190	+10
9	130	+5	23	200	+5, −5
10	130	−5	24	200	−10
11	135	−10	25	210	−10
12	135	−5	26	220	−10
13	140	−5	27	240	−10
14	150	+5	28	250	−5

Except for an occasional complaint of local irritation from too rapidly repeated inhalations, no untoward effects were experienced by the subjects.

The greatest increase in pressure recorded was 10 mm. Hg, which was observed in 4 subjects; the greatest decrease was 15 mm., observed in 1 subject. The majority showed no change or a slight increase or decrease of 5 mm. No consistent change in pulse rate was noted nor did there appear to be any relationship of pulse rate to change in blood pressure.

Discussion. The 20 inhalations so administered should contain, according to the calculations of Simpson and Simon,[17] from 0.4 to 4 mg. of volatile benzedrine base. This moderately acute overdosage was found to raise blood pressure only slightly in a few instances. It would appear that except in extreme overdosage any rise encountered in the therapeutic dose range must be in patients hypersensitive to the compound. Such individual hypersensitivity is occasionally encountered with all sympathomimetic amines.

B. Benzedrine Sulphate. Following its original therapeutic use in narcolepsy,[15] the clinical application of benzedrine sulphate has been greatly extended. It has been used in a wide dose range, the average single dose being 5 to 20 mg. Many observations on the pressor effect of benzedrine sulphate have been made. Alles[1] noted a rise in systolic pressure of 40 mm. after oral administration of 50 mg. in man. The effect appeared to be more prolonged than is usual with drugs of this type.

There appears to be a great variation in pressor effect in different individuals. Myerson, Loman and Dameshek[12] found with 40 mg. taken orally that the increase varied from 8 to 64 mm. systolic; while Davidoff and Reifenstein[3] found with 10 to 30 mg. dosage that systolic pressures varied from an actual decrease to an increase

of 80 mm. Anderson and Scott,[2] Hill[8] and Storz and Kirk[19] observed some increase with 20 mg. Storz and Kirk found no increase in any case with 10 mg., but Hill,[8] and Gwynn and Yater[5] observed increased pressure with this dosage. Smith and Chamberlin,[18] however, state that doses of less than 30 mg. usually cause little increase in blood pressure; and many investigators have reported that there is little increase with 20 mg.[4,16,20,21]

With oral administration the maximum blood pressure effect is usually evident in about an hour and is maintained 2 to 8 hours.

In general, it appears that the lower the initial blood pressure, the greater the percentage increase following an effective dose of benzedrine sulphate. Korns and Randall[9] and Davis and Shumway-Davis[13] used benzedrine sulphate in the treatment of postural hypotension.

Prolonged administration does not seem to change the resting blood pressure,[8,20] although Donley,[4] in treating an agitated depressive, found an increase of 40 to 50 mm. which developed after 2 weeks' therapy; and Lesses and Myerson[10] in treating an obese patient found a decrease from 154 mm. systolic to 104 mm. after 25 weeks' therapy.

Because of the wide variation in blood pressure effects reported, it seemed of interest to obtain additional data on the effects of 10 to 30 mg. oral doses of benzedrine sulphate. Since some authors have felt that the drug might be contraindicated in hypertension, more hypertensive than normal subjects were included in the study.

Results of Oral Administration. Following oral ingestion of benzedrine sulphate in amounts varying from 10 to 30 mg., pressures were taken at regular intervals for a period of 1 hour, and occasionally longer (Tables 2 and 3).

TABLE 2.—BENZEDRINE SULPHATE IN HYPOTENSIVES, NORMALS AND HYPERTENSIVES.

Patient.	Initial pressure.	Maximum variation mm. Hg in systolic pressure.	Time of max. variation in minutes.	Patient.	Initial pressure.	Maximum variation mm. Hg in systolic pressure.	Time of max. variation in minutes.
			Dose, 20 mg.				
1 .	90	+20	30	10 .	155	−5	15
2 .	90	+10	15	11 .	165	+5	15
3 .	95	+5	15	12 .	170	−10	15
4 .	100	−10	60	13 .	180	+20	15
5 .	110	+5	30	14 .	180	−5	15
6 .	115	+5	15	15 .	190	+10	30
7 .	120	0	..	16 .	190	0	..
8 .	120	+10	15	17 .	200	−10	30
9 .	125	−5	30	18 .	220	0	..
			Dose, 30 mg.				
19 .	85	+35	30	9 .	125	+5	15
1 .	90	+30	30	11 .	170	+20	30
4 .	100	+15	60	20 .	170	+5	30
5 .	105	−5	15	21 .	180	+30	60
6 .	115	+10	15	17 .	195	+25	60
7 .	120	+10	30	22 .	195	0	..
8 .	120	+10	15	23 .	200	−10	15

TABLE 3.—BENZEDRINE SULPHATE IN WARD PATIENTS.

Patient.	Initial pressure.	Maximum variation mm. Hg in systolic pressure.	Time of max. variation in minutes.	Patient.	Initial pressure.	Maximum variation mm. Hg in systolic pressure.	Time of max. variation in minutes.
			Dose, 10 mg.				
1	150	−15	45	6	160	+5, −5	45, 60
2	155	−15	45	7	180	+5	30
3	155	−10	45	8	200	−10	30
4	160	+10	30	9	210	+10	60
5	150	−10	30	10	210	−25	60
			Dose, 20 mg.				
3	145	+10	45	7	170	+5	45
11	150	+10	45	15	170	−10	30
12	150	+30	45	16	170	−20	30
13	150	−15	45	17	170	−20	30
14	150	+10	45	18	180	+10	30
4	155	−5	30	19	190	+20	30
5	155	−25	45	8	200	+10, −10	45, 60
1	160	−10	30	9	200	+15	45
2	160	−10	30	10	200	+5	45
6	160	+10	45	20	200	+10	30

Benzedrine sulphate in doses of 20 and 30 mg. was administered to 23 volunteer subjects and ambulatory convalescent recovered hospital patients. Some of them received both amounts.

1. With 20 mg. administered orally, 5 of 18 subjects showed a blood pressure increase of 10 to 20 mm. Two of these were hypertensives. An increase of 20 mm. occurred in only 2 subjects. Three subjects showed a decrease of 10 mm., while the majority showed an increase or decrease of 5 mm.

2. With the 30-mg. dose, 9 of 14 subjects showed an increase of 10 to 35 mm. Three of these were in the hypertensive group. A 35-mm. increase occurred in only 1 patient who had an initial blood pressure of 85. The majority showed an increase of 10 to 25 mm., although 2 subjects showed a slight decrease. In 7 of the 9 who received both 20 and 30 mg., the blood pressure was from 5 to 35 mm. higher with 30 mg. than with 20 mg.; in Subject 8 the effect was the same, and in Subject 5 the blood pressure fell 5 mm. after 30 mg., although it had risen 5 mm. after 20 mg.

The effect of doses of 10 to 20 mg. was observed in 20 hospitalized patients suffering from a variety of diseases (diabetes mellitus, chronic nephritis, malignancy, cardiac decompensation, postoperative convalescence, and so on) who were in nearly every instance confined to bed. They were purposely selected as being in a poor state of health. All exhibited some degree of hypertension.

1. With 10 mg. a rise of pressure of 10 mm. was recorded in 2 of 10 subjects. This was the greatest increase recorded in this group. One subject showed a fall of 25 mm., while the majority showed no change or a slight rise or fall.

2. With 20 mg. there was a rise of 10 to 30 mm. in 10 of the 20 cases. In the only patient showing a 30 mm. increase, the initial pressure was 150. In 8 cases there was a fall of 10 to 25 mm. A decrease of 25 mm. was observed in 1 patient; the remainder showed an increase or decrease of 5 to 10 mm. In the group to whom both 10 and 20 mg. were given, 7 showed an increase of 5 to 20 mm. on the larger dose compared with the smaller; in 1 case the effect was the same, and in 2 cases there was a decrease of 15 mm. compared with the effect of the 10-mg. dose.

When there was a change in pulse rate it was more often an increase than a decrease. No effect on respiration was observed.

Discussion. After the ingestion of 10 mg. benzedrine sulphate by mouth, there is an occasional mild rise in blood pressure; in the present series never over 10 mm. Hg. A greater number (35%) showed an increase after 30 mg.

The data confirm the great variation in pressor response in different individuals found by previous investigators. It seems unpredictable, and does not necessarily vary with sex, age or state of well-being of the subject. Hypertensive bed patients, in a poor state of health, seem to how a greater tendency toward a fall in blood pressure after benzedrine sulphate.

There is apparently a greater tendency for the blood pressure to rise in individuals with a low resting blood pressure than in hypertensive subjects. This suggests confirmation of the rationale of its use in the treatment of hypotension.

Since 20 mg. benzedrine sulphate by mouth gave a rise in blood pressure in only 10% of the hypertensive subjects, it suggests that the clinician should carefully check the blood pressure after the initial dose and discontinue medication if it should have an appreciable hypertensive effect. In the present series, this increase has never been above 30 mm.

The incidence of blood pressure rise seems to increase with increased dosage. As a single dose of 30 mg. gives a significant rise in 35% of the cases, it is apparent that particular care should be exercised in the medication of hypertensive cases in the higher dose range.

Change in pulse rate was inconsistent and bore no apparent relation to change in blood pressure.

Summary. A. Benzedrine vapor was administered to 28 normal and hypertensive subjects by 20 rapid inhalations from the Benzedrine Inhaler, as indicated above.

1. This moderately acute overdosage had little effect on blood pressure.

2. It is concluded that therapeutic doses of the benzedrine vapor should not affect blood pressure except in cases of hypersensitivity.

B. Benzedrine sulphate was administered in doses of 20 to 30 mg. to a group of 23 hypotensives, normals and hypertensives, and in

doses of 10 to 20 mg. to a group of 20 moderately ill patients, most of whom were hypertensives.

1. The incidence of increased blood pressure after administration of 20 to 30 mg. benzedrine sulphate by mouth was, generally speaking, proportional to dosage, but varied with the individual and was apparently independent of the state of the subject's health.

2. Some subjects showed a decrease in blood pressure, in 1 case amounting to 25 mm.

3. With single doses of 10 to 20 mg., a significant rise occurred in 10% or less of the subjects. In hypertension, the drug would not necessarily seem to be contraindicated, but a careful check of blood pressure should always be made following its administration.

4. With doses of 30 mg., the incidence of significant blood pressure increase is considerably greater than with 20 mg. Great care, therefore, should be exercised in treating hypertensives with this dosage.

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BOOK REVIEWS AND NOTICES

INTERNAL MEDICINE. Its Theory and Practice in Contributions by American Authors. Edited by JOHN H. MUSSER, B.S., M.D., F.A.C.P., Professor of Medicine in the Tulane University of Louisiana School of Medicine; Senior Visiting Physician to the Charity Hospital, New Orleans, La. Pp. 1428; 35 illustrations. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $10.00.

THE appearance of the third edition of this excellent work testifies to its acceptance as a standard text in its field. The subject matter has been thoroughly revised to include recent advances and developments, with new material notably on certain infections (undulant fever, tetanus, influenza, streptococcal infections, Haverhill fever, peritoneal tuberculosis, and the contagious diseases of childhood); on gastroscopy and regional enteritis; and on the rapidly expanding field of endocrinology. The volume is the work of 27 contributors (including 3 new ones who replace 2 that have died since the last edition), all of them recognized authorities in their field and, what is even more significant, all experienced as teachers in imparting their information to students. Dr. Musser is to be congratulated on the continued high merit of his text-book. R. K.

A HISTORICAL CHRONOLOGY OF TUBERCULOSIS. By RICHARD M. BURKE, M.D., State Veterans Hospital, Sulphur, Oklahoma. Pp. 84; 1 large graph. Springfield, Ill.: Charles C Thomas, 1938. Price, $1.50.

MORE than 500 events in the history of tuberculosis have been listed in chronological order, the subject being divided into the Ancient Period (up to 1600 A.D.), limited largely to the symptoms of phthisis; the Pre-Modern Period (up to 1800 A.D.), when physicians began examining dead body; and the Modern Period. The first part of the Modern Period (up to the discovery of the tubercle bacilli, 1882) includes the establishment of the unity of the tubercle, knowledge of its histology, and the experimental demonstration of the transmissibility of the disease. The second, and shortest part chronologically, includes the most important items of progress—knowledge of the bacteriology and chemistry of the bacillus and efficient prevention and treatment of the disease. A large folded graphic outline of the development of our knowledge of tuberculosis contains much compact information but is too unwiedly to be handled easily.

The booklet will obviously be useful to the teachers of medicine, lecturers on tuberculosis, superintendents of hospitals, secretaries of tuberculosis associations, public health officers and students of history, for whom it is intended. E. K.

BIOCHEMISTRY FOR MEDICAL, DENTAL AND COLLEGE STUDENTS. By BENJAMIN HARROW, PH.D., Chemistry Department, City College, College of the City of New York. Pp. 383; 52 illustrations. Philadelphia: W. B. Saunders Company, 1938. Price, $3.75.

THIS text contains a great deal of information compressed into a small number of pages. It exemplifies a recent trend in text-books of biochemistry, which is probably natural, though open to criticism—a short text,

made short not by omission but by a cramped "outline" method of presentation. The desire for brevity is apparently at odds with perhaps a stronger desire for inclusiveness. It is, of course, a natural temptation for an author to include as much recent, up-to-date information as possible.

The Reviewer believes that the present work shows good organization of material, and may prove relatively popular as a text. It will not be an "easy" text, however, due to the inclusion of certain details, typified by the following: The empirical formula of carnaubic acid; the structural formula of chaulmoogric acid; a detailed discussion of Bergmann's theory of the frequency in distribution of amino acids in a protein; presentation of equilibrium concepts in enzyme studies. Such details are, of course, of interest to the biochemist and research worker, but in a short text for the student, they lead to confusion. The Reviewer feels that judgment in omission would have improved the text greatly. There is once again a real need for a short text, furnishing essential information of physiological interest, not a compressed long text. Details might well be left to appropriate reference works, which can handle the special subjects at requisite length. D. D.

DISEASES OF THE NOSE, THROAT AND EAR. Medical and Surgical. By WILLIAM LINCOLN BALLENGER, M.D., F.A.C.S., Late Professor of Otology, Rhinology and Laryngology, College of Medicine, University of Illinois, Chicago, etc., and HOWARD CHARLES BALLENGER, M.D., F.A.C.S., Assistant Professor of Otolaryngology, Northwestern University School of Medicine, Chicago; Surgeon, Department of Otolaryngology, Evanston Hospital, Evanston, Illinois, etc. Pp. 1030; 576 illustrations and 30 plates. Seventh Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $11.00.

THIS work can be recommended to student, practitioner or specialist as one of the best available works on Otolaryngology. Changes of and additions to the text of the Sixth Edition, published 8 years ago, adequately cover recent developments in the specialty. K. H.

ESSENTIALS OF PATHOLOGY. By LAWRENCE W. SMITH, M.D., Professor of Pathology, Temple University School of Medicine; Formerly Assistant Professor of Pathology, Harvard Medical College; and, Associate Professor of Pathology, Cornell University Medical School, and EDWIN S. GAULT, M.D., Associate Professor of Pathology, Temple University School of Medicine. With a Foreword by JAMES EWING, M.D., Memorial Hospital, New York City. Pp. 886; 679 illustrations (160 plates, many in color). New York: D. Appleton-Century Company, Inc., 1938. Price, $9.00.

THIS text-book is designed solely for the medical student and presents a rather radical departure from the standard manner of treating the subject of pathology. Emphasis is laid upon those parts of pathology which have a direct and practical clinical application. A brief discussion of the fundamental essentials of each subject is followed by the clinical history of an illustrative case, together with the gross and microscopic pathology exhibited by the organs, with illustrations. Thus, the case-history method of teaching is the basis of this book. It puts into print the more worthwhile features of an orderly series of clinico-pathological conferences.

The book abounds in colored plates and photographs and in addition to the general subject index, there is an index of the case histories and illustrations. Throughout the book are scattered blank pages for the students' personal notes. Believing that students rarely make use of an extensive

bibliography, the authors have omitted this appendage. The achievement of a close relationship between the essentials of pathology and the clinical manifestations of disease should make this an interesting book for the medical student, though it would not seem an adequate substitute for the more conventional student's text-book unless supplemented by very special methods of instruction. D. C.

KLINIK UND THERAPIE DER HERZKRANKHEITEN UND DER GEFÄSSERKRANKUNGEN. VORTRÄGE FÜR PRAKTISCHE ÄRZTE. By DR. D. SCHERF. Privatdozent in Vienna. Pp. 319; 10 illustrations. Fourth edition. Vienna: Julius Springer, 1938. Price, Paper, Rm. 7.20; Bound, Rm. 8.40.

THE author points out that he has not produced a textbook and does not cover all cardiovascular subjects, although the most important diagnostic and therapeutic problems have been stressed. The book is more representative of the best European Continental current thought and practice than any other recent publication which has come to this Reviewer's attention. It should interest the American physican who reads German easily and who wishes to supplement what our own writers of textbooks have to say by acquainting himself with the views of others. The discussion of treatment contains a number of excellent suggestions. C. W.

HUMAN PATHOLOGY. A Textbook. By HOWARD T. KARSNER, M.D., Professor of Pathology, Western Reserve University, Cleveland, Ohio. With an Introduction by SIMON FLEXNER, M.D. Pp. 1013; 461 illustrations (18 in color). Fifth edition, revised. Philadelphia: J. B. Lippincott Company, 1938. Price, $10.00.

IN the 3 years that have elapsed since the appearance of the fourth edition of this well-known textbook, pathology has progressed enough to demand considerable textbook revision. "No chapter of the book has escaped alteration. The discussion of pathological pigmentations now emphasizes the significance of pulmonary silicosis. Fatty metamorphosis is presented in the light of much recent study. Amyloidosis has been reclassified and the discussion clarified. In the section on circulatory disturbances, the newer views of edema, thrombosis and pericardial adhesion have been included. There is also new material in the study of inflammation and of tumors." Other topics altered are the sections on circulatory disturbances, cardiovascular and pancreatic diseases, and those of the hematopoietic, respiratory and nervous systems. As previously, the extensive references provide easy approach for the ambitious student to a more extensive study of any subject in which he is particularly interested. This edition retains its position as unquestionably one of the leading textbooks of the subject in a language which is singularly well endowed with one-volume books in this field. E. K.

CLINICS ON SECONDARY GASTRO-INTESTINAL DISORDERS; RECIPROCAL RELATIONSHIPS. By JULIUS FRIEDENWALD, M.D., Professor Emeritus of Gastro-Enterology, THEODORE H. MORRISON, M.D., Clinical Professor of Gastro-Enterology, and SAMUEL MORRISON, M.D., Assistant Professor of Gastro-Enterology, all of the University of Maryland, School of Medicine. Pp. 251. Baltimore: William Wood & Co., 1938. Price $3.00.

IN this volume the authors have pointed out the high incidence of secondary gastro-intestinal disorders occurring in diseases originating outside of

the digestive tract. Cardiovascular disease, pulmonary tuberculosis, focal infection, genito-urinary affections, endocrine disorders, syphilis, various deficiency states, diseases of the nervous system, skin and eyes are considered from this standpoint. The general thesis is an important one, and a compilation such as this has much virtue. The chief value of the present volume, however, is that of a catalogue. Written in the didactic manner of earlier clinical presentations, it contains many statements which will be challenged by the experimentally minded clinician. As a descriptive work, though somewhat diffuse, it contains a great deal of value; as a stimulus to clinical investigation it is scarcely provocative. K. E.

LABORATORY MANUAL OF HEMATOLOGIC TECHNIC. By REGENA COOK BECK, M.A., M.D., Formerly Instructor in Pathology and Bacteriology at George Washington University Medical School; Head of the Department of Bacteriology, William and Mary College Extension, etc. With a Foreword by FRANK W. KONZELMANN, M.D., Professor of Clinical Pathology, Temple University, Philadelphia. Pp. 389; 79 illustrations. Philadelphia: W. B. Saunders Company, 1938. Price, $4.00.

CAREFULLY planned for the student technician, Dr. Beck's manual will also prove a valuable *vade mecum* of hematologic methods for experienced technicians, medical students practicing physicians and instructors. The selection of techniques is sound, the range is comprehensive, and the material is up to date. The style is clear and terse. Of particular value are the sections dealing with bone marrow examination, vital staining, the various erythrocyte and leukocyte indices and the hematology of exudates, transudates, and spinal fluid. The illustrations are adequate despite the absence of colored plates. Review questions and a glossary of hematologic terms are useful teaching features. A foreword by Dr. F. W. Konzelmann is justly laudatory. Your Reviewer heartily recommends this manual. T. F-H., JR.

CAUSES OF CRIME. Biological Theories in the United States, 1800-1915. By ARTHUR E. FINK, Department of Sociology, University of Pennsylvania. Pp. 309. Philadelphia: University of Pennsylvania Press, 1938. Price, $3.00.

AFTER commenting on the lack of appreciation here and abroad of the work done by American students on human behavior, the author proceeds to a discussion of the period from 1800 to 1915, under the following headings: Phrenology; Insanity; Moral Insanity; Alcohol and Drugs; Criminal Anthropology—I. Anatomy of the Criminal; II. Physiology of the Criminal; heredity—The Jukes; Human Sterilization; Feeblemindedness; Conclusion.

Some mention is made of the prisoner described by Charles Dickens in *American Notes*, for whom much sympathy was created here and abroad. At times, when dealing with facts, Dickens' exuberant imagination tended toward pseudologia phantastica. In 1841, Dickens visited the Eastern State Penitentiary and later described conditions there as devastating in their effects upon the inmate mind and body. Of one prisoner with whom he talked, who was subsequently known as "Dickens' Dutchman," he wrote: "A more dejected, broken-hearted creature it would be difficult to imagine. I never saw a picture of more forlorn affliction and distress of mind. My heart bled for him . . . I never saw or heard of any kind of misery that impressed me more than the misery of this man."

The Reviewer obtained the following information from the Penitentiary. Dickens died in 1870 and the prisoner was alive 15 years later. The prison

record continues: "When the novelist saw the German thief, he was serving his second term in the Penitentiary. Since then has served 12 more, or 14 in all, in the same institution. I once saw him in Quarter Sessions after he had been sentenced to a brief imprisonment in the County Prison. With tears pouring down his cheeks he begged to be sent back to the Penitentiary even though his time had to be doubled. His request was granted." The record ends with this comment: "Solitary confinement which permits people to die of old age, cannot be such a dreadful thing."

A recent writer, an extensive employer of labor, states he will never employ an ex-convict, even though unjustly imprisoned; not because he has "done time," but because of personality change consequent upon incarceration; but, he adds, if the last year of detention were spent in a prison camp or some other extra-mural environment, his objection would be overcome. Work need not so often be denied ex-convicts: The Ford Motor Company will accept, without discrimination, all former inmates who have worked in the mechanical department of the Federal Industrial Reformatory, Chillicothe, Ohio. Careful study of crime in the light of present-day knowledge, would be instructive. Keep politics—not politicians—out of prisons. Provide more and better officers to supervise those on probation or parole. Have the last year of a long sentence spent in a prison camp. Act upon the recommendations of the recent Wickersham Committee. The writings of Sanford Bates, and many others since 1915, will be found revealing as to causes of crime and of ways to lessen some of them.

N. Y.

MATERNAL CARE COMPLICATIONS. The Principles of Management of Some Serious Complications Arising During the Antepartum, Intrapartum, and Postpartum Periods. Edited by F. L. ADAIR, M.D. Approved by The American Committee on Maternal Welfare, Inc. Prepared by R. D. MUSSEY, M.D., P. F. WILLIAMS, M.D., F. H. FALLS, M.D. Pp. 95. Chicago: University of Chicago Press, 1938. Price, $1.00.

WITH the increasing emphasis which is being given to attempt to reduce our unnecessarily high maternal mortality, the volume by Adair and his co-workers on Maternal Care Complications ought to fulfill a very useful purpose. Only three subjects are discussed, toxemias of pregnancy (written by R. D. Mussey), obstetric hemorrhages (by P. F. Williams), and puerperal infection (by F. H. Falls).

Each subject is well covered, emphasis being evenly distributed between pathology, diagnosis and treatment. The book contains no new information, but as the editor states in the preface: "This . . . volume attempts to present the essential facts relative to the three major causes of maternal mortality."

The small size of the book, its style, and the importance of its contents ought to give it a large field of usefulness. It would be well if a copy could be placed in the hands of every medical student and interne. D. M.

HUMAN UNDERSTANDING AND ITS WORLD. A Study of Societies. By By K. W. MONSARRAT, Consulting Surgeon, Northern Hospital, Liverpool; formerly Dean of the Faculty of Medicine, University of Liverpool. Pp. 480; 42 figures. London: Hodder & Stoughton, Ltd., 1937; Liverpool: The University Press, 1937. Price, 15/-.

THE author of this work—a distinguished English physician and surgeon—despite a busy life of practice and teaching has found time heretofore to publish a volume of poetry as well as a number of essays on philosophical

topics. *Human Understanding and Its World* is probably the most substantial of the author's contributions to the borderline of medical literature.

The present volume is really a remarkable work, implying, as it does, a competence in sociology, anthropology, philosophy, particularly epistemology, and the physical and biological sciences, particularly physics and psychology. The book is of professional interest to students of these disciplines.

The subject treated is the historic problem of finding a place for human understanding in a theory of nature. The author shows it to be a double problem: first, the question of the rôle of human understanding in the development of theories of nature; and second, the more fundamental question of the grounds upon which the human mind can be regarded as a phenomenon consistent with the kind of theory developed. The author's method is both historical and critical. In the first section he reviews a number of the theories of nature developed during historic times, such as those developed by the genuine primitives, Amerindians and Australians, as well as those of civilized cultures, Jews, Greeks, Romans and early Christians. While the author pretends to no original contribution in these chapters, his writing rests upon an impressive scholarship. The theory to which Monsarrat devotes the greater part of his narrative is, however, one developed by the use of the experimental method. The principal relevant features of the contributions of the physical and biological sciences are reviewed in considerable detail. There is, for example, a lengthy description of the quantum mechanics as well as a considerable discussion of the organismic hypothesis as it appears in the various biological sciences. The final sections of the book treat of the problem of showing the activity of the human understanding to be consistent with the picture of nature developed by the experimental scientist.

Monsarrat's principal conclusion from the examination of the evidence from the history of cultures is that the theories of nature obtaining among peoples who lived prior to the time of the Greeks were: "a type of human reaction which proceeds to the formulation of a picture of the world in which discrimination is minimal," and that: "the elementary apprehensions which (were) used in its construction (were) formed with a minimum of reference to any standard of classification other than that of human like and dislike" (p. 12). With the Greeks appeared the first intimation of intellectual discrimination; from that time until the present, the importance of the pure intellectual operations in the development of ideas concerning nature became transcendent.

We must not suppose, however, that the products of experiment are invariably a unique and sufficient guide to the development of the theory. A most striking example of experiment confusing the theorist is the celebrated conclusion of Heisenberg that it is impossible to determine simultaneously the velocity and position of the electron. Monsarrat believes that this experiment, and the enunciation of the principle associated with it, illustrate two kinds of improper questions addressed to nature.

"The mathematician (Heisenberg) concerned himself with the fact that when he treated the electron *ideally* as a particle in the service of classical mechanics, he could make no precise statement about its position and velocity simultaneously. The first remark we make is the impropriety of asking any question which treats the participants in events singly. This question about the behaviour of the electron followed upon another already asked and answered—namely, 'What is an electron?' Answer, 'A particle.' But nothing whatever can be said of any participant in events when it has been isolated in this manner; all that can ever be said of any factor concerns its behaviour *vis-a-vis* another, and any question which involves a preliminary 'treating as' is vitiated at its beginning. This 'treating as' may, of course,

be used hypothetically, and the question may then be asked 'Does the electron behave like this other which I have defined and named a particle?'; but when the answer is 'No' the next step is not the enunciation of a principle, but the asking of a different question" (pp. 233–234). The second kind of improper question involves a less subtle argument. This question yields no answer because of certain natural circumstances which obtain in the relations between observer and observed. In the case of the quantum mechanics: "the difficulties encountered are to be assigned to the fact that except for certain facts as to structure, the state of affairs in the atom can only be inferred from radiation behaviour, and is imperfectly told by this" (p. 239).

The first improper question discussed by Monsarrat introduces a further consideration of non-experimental factors contributing to the development of an image of nature. In the first place the author takes the position that the work of the scientist (and of course of the natural philosopher) consists in describing phenomena. Monsarrat is opposed to the notion that events can be explained. Explanation involves abstraction which in turn leads to such absurdities as the first of the improper questions listed above. In the second place the author believes that the separate sciences each do no more than contribute detail to the larger picture of what might be called the total state. In the third place the definition of the total state falls completely outside the realm of experimental science because it depends upon the acceptance of one philosophical position on the mind-body problem, and the rejection of the others. Monsarrat accepts the so-called double-aspect theory of mind and body, rejecting explicitly the theory of psycho-physical parallelism and implicitly the pure idealism to which his reflections appeared at times to be leading him. The place of human understanding in the image of nature is thus guaranteed; the validity of its study is supported by a series of arguments concerning the distinctions between knowledge of our own minds and the minds of others. These arguments appear to rest upon an acceptance of the historic argument from analogy. The single concept which gives unity to the world-image is the dynamic concept of power. A final section extends the consideration to the problems of social psychology and of history.

While it is hazardous to attempt more than a tentative evaluation of this remarkable book, its obvious strength and weakness may be mentioned. Its scholarship is impressive. The recognition that experiment alone is no sufficient guide to our knowledge of nature gives evidence of a careful, penetrating reflection upon the problem of knowledge. The position occupied by Monsarrat in this respect is indeed far from that taken by many experimental scientists who are completely naive in the field of epistemology, and is one which is becoming more and more recognized by those scientists who are concerning themselves with the philosophy of science. One cannot help feeling that a wide gulf separates those who believe that Heisenberg's experiment is important because of the methodological question it raises and those who believe it to be important because, as Monsarrat writes, it seems to impute a kind of perverse untrustworthiness to the atom. His analysis of societies in respect of their images of nature is a valuable addition to the literature of the subject, and one which, it might be hoped, will lead others to amplification of the detail.

We believe the weakness of the work to be implicit in the acceptance of the theory that the manifestations of mind and of body constitute two aspects of the same thing. The argument from analogy gives only apparent support to the proposition that we may have knowledge of minds other than our own. The demonstration that the argument is fallacious unhappily leads to a solipsism, provided no new attack is made on the main problem.

There is much which may be said against the proposition that scientists

are not explainers, particularly if explanation is defined as the operation of subsuming observations under laws. While it is true that the definition of scientific law is a formidable task, we do not believe it to be insurmountable, provided recognition is made in the rôle of choice and motive in the work of the experimental scientist. We might finally point out that the concept of power formulated in the closing sections of the work is one which the experimental scientist would have great difficulty in applying to the investigation of the problems of social psychology and of history. We should pause to point out that at least one historian, Henry Adams (The Education of Henry Adams), has already remarked on that difficulty in the case of a similar concept. M. P.

NEW BOOKS.

Cardiovascular Disease in General Practice. By TERENCE EAST, M.A., D.M. (OXON.), F.R.C.P. (LOND.), Physician and Physician-in-Charge of Cardiological Department, King's College Hospital; Physician, Woolwich War Memorial Hospital, etc. Pp. 206; 43 illustrations. London: H. K. Lewis & Co., Ltd., 1938. Price, 10s. 6d.

Spinal Anesthesia. By LOUIS H. MAXSON, A.B., M.D., Practicing Specialist in Anesthetics; former Chief Anesthetist, Harborview (King County) Hospital, Seattle. Foreword by W. WAYNE BABCOCK, M.D., LL.D., F.A.C.S., Professor of Surgery, Temple University School of Medicine. Pp. 409; 69 illustrations. Philadelphia: J. B. Lippincott Company, 1938. Price, $6.50.

Chirurgie der Lungen und des Brustfelles. (Band 26 of Medizinische Praxis, Sammlung für Ärztliche Fortbildung, Herausgegeben von Prof. Dr. L. R. Grote, Prof. Dr. A. Fromme and Prof. Dr. K. Warnekros.) By DR. ALFRED BRUNNER, Chirurg. Chefarzt am Kantonsspital St. Gallen; Früher Privatdozent für Chirurgie und der Universität München. Pp. 282; 112 illustrations. Dresden: Theodor Steinkopff, 1938. Price, Paper, Rm. 22.50; Bound, Rm. 24.00.

Teachable Moments. A New Approach to Health. By JAY B. NASH, PH.D., Professor of Education, Chairman of the Department of Physical Education and Health, School of Education, New York University. Pp. 243. New York: A. S. Barnes & Co., 1938. Price: $1.50.

Carbon Monoxide Asphyxia. By CECIL K. DRINKER, M.D., D.Sc., Professor of Physiology and Dean, School of Public Health, Harvard University. Pp. 276; 40 illustrations, and 21 tables. New York: Oxford Univerity Press, 1938. Price, $4.50.

The Physiology of Anesthesia. By HENRY K. BEECHER, A.B., A.M., M.D., Instructor in Anesthesia, the Harvard Medical School; Anesthetist-in-Chief, the Massachusetts General Hospital. Pp. 388. New York: Oxford University Press, 1938. Price, $3.75.

Marihuana. America's New Drug Problem. A Sociologic Question with Its Basic Explanation Dependent on Biologic and Medical Principles. By ROBERT P. WALTON, Professor of Pharmacology, School of Medicine, University of Mississippi. With a Foreword by E. M. K. GEILING, Professor of Pharmacology, University of Chicago, and a Chapter by FRANK R. GOMILA, Commissioner of Public Safety, New Orleans, and M. C. GOMILA LAMBOU, Assistant City Chemist. Pp. 223; 13 illustrations. Philadelphia: J. B. Lippincott Company, 1938. Price, $3.00.

Practical Birth Control Methods. By NORMAN E. HIMES, PH.D., with the medical collaboration of ABRAHAM STONE, M.D. Introduction by ROBERT L. DICKINSON, M.D., Foreword by HAVELOCK ELLIS. Illustrations by IRVING GEIS. Pp. 254; 29 illustrations. New York: Modern Age Books, Inc., 1938. Price, 95c.

The Medical Clinics of North America, Vol. 22, No. 6 (Philadelphia Number, November, 1938), Index Number. Pp. 301; 21 illustrations. Philadelphia: W. B. Saunders Company, 1938.

NEW EDITIONS.

The Surgery of Oral and Facial Diseases and Malformations. Their Diagnosis and Treatment Including Plastic Surgical Reconstruction. By GEORGE VAN INGEN BROWN, D.D.S., M.D., C.M., F.A.C.S., Emeritus Professor of Plastic Surgery, University of Wisconsin; Sometime Professor of Oral Surgery and Oral Pathology, State University of Iowa, and Special Lecturer on Oral Surgery, University of Illinois, Vanderbilt University and Atlanta-Southern Dental College, etc. Pp. 778; 589 engravings containing 1019 illustrations and 12 colored plates. Fourth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $10.00.

Manual of Veterinary Bacteriology. By RAYMOND A. KELSER, D.V.M., A.M., PH.D., Lieut. Colonel, Veterinary Corps., United States Army; Chief, Veterinary Division, Surgeon General's Office, War Department, Washington, D. C., etc. Pp. 640; 93 illustrations and 11 tables. Third Edition, thoroughly revised. Baltimore: The Williams & Wilkins Company, 1938. Price, $6.00.

Practical Otology. By MORRIS LEVINE, M.D., F.I.C.S., Clinical Professor of Otolaryngology, New York Post-Graduate Medical School, Columbia University; Attending Otolaryngologist, New York Post-Graduate Hospital. Pp. 416, 146 illustrations and 3 colored plates. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $5.50.

Synopsis of Clinical Laboratory Methods. By W. E. BRAY, B.A., M.D., Professor of Clinical Pathology, University of Virginia; Director of Clinical Laboratories, University of Virginia Hospital. Pp. 408; 51 illustrations and 17 color plates. Second Edition. St. Louis: The C. V. Mosby Company, 1938. Price, $4.50.

Physical Diagnosis. By RICHARD C. CABOT, M.D., Professor of Clinical Medicine Emeritus in Harvard University; formerly Chief of the West Medical Service at the Massachusetts General Hospital, and F. DENNETTE ADAMS, M.D., Instructor in Medicine in the Harvard Medical School, Courses for Graduates; Associate Physician at the Massachusetts General Hospital. Pp. 846; 391 illustrations. Twelfth Edition. Baltimore: William Wood & Co., 1938. Price, $5.00.

Clinical Laboratory Methods and Diagnosis. A Textbook on Laboratory Procedures with Their Interpretation. By R. B. H. GRADWOHL, M.D., Director of the Gradwohl Laboratories and Gradwohl School of Laboratory Technique; formerly Director of Laboratories, St. Louis County Hospital, etc. Pp. 1607; 492 text illustrations and 44 color plates. Second Edition. St. Louis: The C. V. Mosby Company, 1938. Price, $12.50.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE.

UNDER THE CHARGE OF
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ALTERNATION OF THE HEART.

SINCE Traube[38] first described pulsus alternans in 1872, an extensive literature has developed on the subject. Interest has been more widespread upon the Continent, where it culminated, in 1930 and 1932, in the appearance of several monographs[19b,33a] dealing extensively with all phases of the subject. Reports since that time, still predominantly European, have added somewhat to our understanding of the fundamental causes of alternation and have clarified certain aspects of the problem. With these more recent reports the present review is chiefly concerned and older contributions will be cited only as they are necessary in the interpretation of newer data.

The term, *pulsus alternans*, indicates an alternation in the force or strength of the pulse, in the presence of a regular cardiac rhythm, arising usually in the normal pacemaker. As Mines states,[26] it is a condition in which cardiac muscle is acted upon by evenly spaced stimuli (either natural or artificial) and responds with alternate large and small contractions. The term implies that the cause of the irregularity rests inherently in the heart—that such extraneous influences as respiratory changes in the pulse are not primarily the cause of the disturbance. Pulsus alternans is, then, an index of disturbed function in the left ventricle and may be used as a sign of defective action of that heart chamber. Since clinical and animal investigations[5] have demonstrated similar disturbances in the auricles, the right ventricle, and the hemodynamic functions dependent upon these parts, the more inclusive term, *alternation of the heart*, the *herzalternans* of the Germans, is commonly used to cover in general all the phenomena of alternation related to the heart. The auricles and ventricles may be involved singly or together, either discordantly or concordantly.[22a]

Mechanism of Alternation. Results of experimental observations have led to many theories of alternation, but these have been reduced to two general groups, first those in which all muscle fractions contract either in different or equal degrees, but with a slower phasic entry of contractions in the smaller beats, so-called *hyposystole;* and second, those concerning the failure of certain fractions of muscle to contract on alternate beats, so-called *partial asystole.*[43a]

Katz and Feil[16] stress the factors concerned in the former group, with the alternating dynamic changes of the heart produced by constantly occurring fluctuations in the circulation. As they point out, the exact cause and effect relationship is not agreed upon by the exponents of this view,[36,40,43b] which was first postulated by Wenckebach. If it is assumed that the first small beat puts out a reduced volume of blood, leaving an increased systolic remainder, in the next beat there is an increased initial volume and tension in the ventricle, emptying it beyond normal. The residue is then reduced and a small beat follows, the cycle continuing for a variable time. The large pulse following an extrasystole, a sudden change in rhythm, and marked variations in respiration may also initiate alteration in the initial tension and diastolic volume of the ventricles and have the same effect as the small pulse of alternation. Also since diastolic pressure (the resistance to emptying) is less in the diastole preceding the large pulse than in the one preceding the small pulse, the diastolic pressure tends to hinder the emptying of the small pulse and permits greater emptying of the large pulse. The results of Katz and Feil are in agreement with such a concept and, in general, fit with those found by other observers in experimental alternation.[15,43b] The observations relative to such dynamic changes are interesting and important in that they were carried out, not on experimental alternation in animals but upon 5 clinical cases. All consistently showed, associated with the alternating pulse, an alternation in the intensity of the heart sounds, in the duration of the isometric and ejection phases, and in the pulse gradient. The duration of total systole and of previous diastole showed no consistent alternation, although slight changes in diastole insufficient to produce dynamic changes were noted. Measurements of the various diastolic phases were not made. In systole, isometric and ejection phases alternated discordantly with prolongation of the isometric and shortening of the ejection phase in the small beats. Thus the duration of total systole was relatively constant. The pulse gradient alternated concordantly with the size of the pulse. Such results do show that the alternation is not the result of alternation in the duration of diastole, a finding which differs from the experimental results of Wiggers,[43b] although the importance of changes in the phases of diastole are not excluded.

These results do not exclude the possibility of the failure of certain fractions of muscle to contract to cause pulsus alternans. The authors make it clear that they have not proved that dynamic changes of one beat alone produce the dynamic changes in the next beat and so perpetuate the pulsus alternans, nor that the circulatory changes initiate pulsus alternans mechanically. Yet it was upon the basis of the possible effects of such hemodynamic changes on the ventricular filling and diastolic tension that Wenckebach[40] concluded that certain instances of alternation of the pulse might be due to alternate deficiencies in ventricular filling and subsequent ejection. In such instances he thought the sign might not be indicative of grave myocardial damage with a bad prognosis. Although this view is not generally held today, it is indeed true that clinical experience[22b] has shown that such a prognostic outlook is not to be expected when alternation results presumably from fatigue phenomena dependent on extreme tachycardia. A clinical problem demonstrating the point in question, occurring at a slow heart rate,

is the case report of Nussbrecher.[30] In this patient, palpation of the apex or radial artery disclosed a sequence of strong beats followed by two weaker ones, the second weak beat appearing somewhat premature. The blood pressure at the three systolic levels was 210, 180 and 160 mm. of mercury, respectively, with one-third, two-thirds and all the beats coming through at the respective levels. One might offer as an explanation for these findings, as Nussbrecher suggests, that the compensatory pause following the premature contraction allowed good filling of the ventricle producing a strong beat following it. However, the next normal beat had only the normal time for ventricular filling and, compared to its predecessor, was relatively weak. Such an explanation of the mechanism of alternation in this patient is similar to those just given, and did not require, as Nussbrecher states, the assumption of partial ventricular asystole. It would, therefore, reduce the prognostic significance of the finding even though the patient had heart disease. He cites a similar case described by Gravier.[9]

The experimental observations of Wiggers[43b] favor the same school of thought and the findings are compatible with such dynamic explanations. He noted, while working on the dynamics of ventricular extrasystoles, that the beat following a large compensatory contraction was often smaller than normal, and that frequently the next few beats showed alternation which gradually diminished and disappeared. The heart muscle was presumably normal in every respect, and the alternation was conditioned entirely by the rate, not being present in normal hearts below the rate of about 140 per minute. Like other types of alternation, the smaller beats showed a slow rise in pressure with a longer isometric and shorter ejection phase than the larger beats. At the beginning of the small beats diastolic size was less and the initial tension lower, results entirely compatible with the explanation of secondary effects of alternate ventricular filling. For details of these observations the reader is referred to the original paper.[43b] Such temporary alternation clinically, Wiggers felt, may not be due to primary derangement of the cardiac muscle and so would not presage the development of a more permanent type.

Despite the fact that all these observations appear to be compatible with a dynamic theory of pulsus alternans, none proves the cause and effect relationship of the findings and none rules out the possibility of the failure of contraction of certain muscle fibers as the cause. The latter is the most favored view at present. It is favored by the experimental production of alternation of the heart, demonstrated many times, by actual injury or poisoning of the heart by various chemicals, such as aconitine,[5] digitalis,[29] glyoxalic acid,[15] and other chemicals,[25] as well as following exposure and manipulation of the heart,[5] impairment of blood supply, as in interference with coronary circulation, nervous influences,[25,29] and production of tachycardias. Actual cardiac damage or factors predisposing to cardiac fatigue appear at work in all these procedures. Such observations raise the question whether pulsus alternans as seen in the clinic is always analogous to the experimental type and whether it also must always rest upon serious impairment of myocardial function.

In 1882, Gaskell,[8] working on the cold blooded heart, concluded that when the ventricle alternates a partial asystole occurred with the

smaller contraction dependent upon a lowered excitability of certain fibers which respond not to every beat but to every other beat. There is, then, in this view no failure to conform to the all or none law, for certain fibers did not respond at all. Hering[13] carried out his observations on the mammalian heart and reached similar conclusions. He felt that groups of fibers remained in a prolonged refractory period, permitting response only to every other cardiac cycle and resulting in partial asystole at the time of the smaller contraction. Whether this failure to contract may be confined to the time of the smaller contractions or occurs in both contractions but to a greater extent in the smaller beats is a matter of controversy. Mines[26] favors the latter view and sees no reason to expect that the portions of the muscle exhibiting asystole should form circumscribed masses. Such fibers may be distributed throughout the myocardium as well as occurring in circumscribed areas. Other theories besides the prolongation of the refractory phase have been proposed as possible causes of failure of fractions of the myocardium to contract. These include a reduction in irritability of these fibers to a level where the natural stimulus becomes subminimal and the incidence of local blocks which prevent the impulse from reaching these fractions.[43a] Many of these controversial topics have been treated by Lewis.[22c]

The observations of Green[10] from Wiggers' laboratory are pertinent to the view of asystole. In dogs, he reduced the blood supply to a portion of the myocardium by intermittent clamping for short intervals of a main coronary artery. The vessel was occluded with an electromagnetic clamp for one-half to two-thirds of each heart cycle and occasionally for 2 or 3 cycles out of every 5 or 6, impairing the blood supply but not completely suppressing it. Alternation appeared in a fair number of hearts. Optically recorded myocardiograms from the affected areas showed that these portions of the myocardium did not contribute to ejection in the smaller beats and either contracted inadequately or only sufficiently to prevent stretching of the area by the increased intravascular tension. Since it seems reasonable to assume that the portion of the myocardium having an unimpaired blood supply should contract normally, Green feels that the alternate missing of contractions in the ischemic area is undoubtedly responsible for the alternating pulse shown in the aortic pressure curves. Demonstration was made in 2 curves also that contractions not only failed in the ischemic area in the smaller beats, but those that occurred in the larger beats were less vigorous. Thus it has been shown in the mammalian heart that impaired circulation may institute the occurrence of alternation and that when the failure of contraction is limited to one portion of the heart the alternation produced in the pulse cannot be distinguished from alternation involving the entire myocardium of the left ventricle. In applying these results to the theories of alternation, one can see that alternate contraction and failure to contract of segments of the myocardium, either large, or multiple and small, must be considered as a possible cause of clinical alternation either of the left ventricle or the whole heart. Since pulsus alternans is seen frequently at normal heart rates in patients with coronary changes, this mechanism is a most likely one, possibly involving multiple small areas in diffuse sclerosis and a large segment or segments in acute infarction. Yet the demonstration

of alternation following clinical acute myocardial infarction[22a,37] is not *a priori* evidence that the segment of myocardium involved is alone responsible for the alternation, for, unlike in experimental animals, the coronary arteries of clinical cases with infarction may be inadequate in other portions of the heart, particularly in the stage of shock, and these portions of the heart may also contribute to the alternation detected in the pulse.

Certain of Green's observations are also important in evaluating the hemodynamic changes already given above. Myocardiographic records in dogs with both extrasystoles and impaired coronary flow showed that in the alternation following extrasystoles inherent changes in the muscle are probably important, for contraction changes occurred in alternate beats. He suggests that the relationship to changes in initial tension and length found by Wiggers are probably fortuitous and not to be regarded as fundamental determinants of alternation. The time required for recuperation rather than the dynamic changes is the factor probably dominantly concerned in producing this temporary type of alternation. Wiggers was careful to state that such dynamic factors cannot be held accountable for permanent alternation seen clinically. With the additional information added by his observations, Green questions whether any form of alternation can occur without periodic diminution or absence of contraction in some fractions of the ventricular muscle.

Clinical Aspects. The clinical aspects of pulsus alternans are concerned most importantly with its recognition and differential diagnosis, as well as its clinical significance in diagnosis and prognosis.

Recognition. There are no subjective symptoms referable to pulsus alternans *per se*. Since it is a manifestation of left ventricular damage, it will be found in those individuals displaying symptoms of disease affecting that chamber of the heart, especially angina pectoris, coronary thrombosis, aortic regurgitation, and congestive heart failure from other causes.

The methods of eliciting pulsus alternans are too well known to deserve comment. Most commonly used is that employing the blood pressure cuff. Since the systolic pressure is higher in every other beat, as the cuff pressure, previously raised above the systolic level, is lowered, at one level every other beat comes through, and as the pressure is further lowered until the second systolic level is reached, all beats come through; that is, the number of beats coming through is suddenly doubled. The degree of alternation can be expressed in millimeters of mercury difference in the two systolic levels. This may vary from about 2 mm. of mercury to the pulse pressure of the beats with the higher systolic level in most extreme grades. In the latter instance no, or little, blood is put out and consequently no, or only a slight, pulsation is produced by the weak contraction. The pulse is then slow and at half the cardiac rate. The more extreme grades of pulsus alternans are recognized by palpation alone, but this method of examination becomes useless in the minor grades.

There is one other method of recognition of pulsus alternans in common use. That is the arteriogram, or pressure pulse tracing of the radial or any other artery. This latter method requires the use of a piece of apparatus not possessed by most physicians; and, according to

White and Lunt,[42] the alternation usually must be in the neighborhood of 6 mm. of mercury before it is descernible in the ordinary radial tracing, whereas an alternation of 2 mm. of mercury may be found by use of the sphygmomanometer.

The frequency of pulsus alternans, particularly the transient variety, is difficult to estimate. White[41a] found it as frequently as auricular fibrillation. In an 8 months' study at the Massachusetts General Hospital, he found alternation of the pulse in 33% of all patients showing any degree of cardiac decompensation from whom a radial pulse tracing was obtained. Such tracings showed alternation in 71 of 300 patients with cardiac or cardiorenal disease. Yet reports stress its rarity, indicating that the frequency with which it is sought when blood pressure determinations are made is very low.

A sign as important both diagnostically and prognostically as alternation of the pulse should be sought for in all patients suspected of heart disease. Because practically every physician carries routinely to the bedside all the equipment necessary to make this test and because the procedure for establishing the presence or absence of pulsus alternans is carried out on these patients anyway when the blood pressure is taken, the lack of recognition of this sign lies either in ignorance or in negligence. It should be sought for deliberately in all patients suspected of heart disease when the blood pressure is taken. This is particularly true in the middle aged and elderly patient, for it is most frequent in those with hypertension, coronary sclerosis with and without angina pectoris or coronary thrombosis, as well as in other types of heart disease. For example, in one series,[37] 71 patients with pulsus alternans died of cardiovascular disease. With the exception of 6 patients with rheumatic heart disease and 2 with heart disease of unknown etiology, all had either hypertensive cardiovascular, or coronary artery disease. Hypertension was present in 81% of these patients and in 2 with rheumatic heart disease, making a total of 83% with hypertension. In this class of patient particular care should be taken to search for alternation following isolated premature beats, for it may present itself only at that time. Repeated search in subsequent visits should be made. It should also be remembered that alternation may occur at the systolic level and the diastolic level either singly or at the same time.

It is generally stated that the detection of alternation in the heart sounds by auscultation over the precordium is rare. White[41a] found no significant changes in heart sounds and others have reported similar findings. Such statements have not gone unchallenged. As early as 1905 Volhard[39] reported recognition of alternation of the heart tones with accentuation of these changes following premature beats. With the large pulse beats the intensity of the sound was increased and the pitch became higher. Katz and Feil[16] found a concordant alternation of heart sounds in their patients. The second sound was less intense in all subjects and shorter in duration in one in the smaller beats. In 2 cases a third heart sound showed alternation, more intense in the diastole preceding the small beat. Morris[28a,b] found, in 38 patients with permanent alternation, that one-half the patients displayed an alternation in intensity and pitch of heart sounds or murmurs or both. He found these changes sometimes in the first or second sound at the apex

and at times in other valvular areas. Rarely both (first and second sounds) alternated together. More recently Cossio, Lascalea and Fongi[4] have confirmed the findings of Morris by use of phonocardiographic records. In 7 patients with pulsus alternans they found alternation of the heart sounds—in 4 the first sound and in 3 both sounds. They found, however, and this may be partially responsible for the lack of recognition of auscultatory changes, that the alternation was not constant. It occurred only at certain moments and seemed to disappear at other times. They noted further that single premature beats were followed by conspicuous alternation of the sounds as a rule.

The known abruptness of the elevation in intravascular pressure in the beginning of systole of a large beat would be expected to increase the intensity of the first sound in this beat as compared to the intensity of the same sound in a small contraction, when the rise of intravascular pressure is gradual. The same relationships in the fall of pressure at the end of systole would be expected to produce the same relative changes in the second sound of each beat. However, these observers found the reverse relationship in regard to the second sound and cite a similar case in the literature. The discordant character of the second sound they ascribe to a greater impairment of conduction of the sound to the chest wall at the end of the strong beat when the heart is actually smaller (more contracted).

Both of these groups of investigators stress the fact that alternation of the sounds must be carefully listened for or it will be missed. "The acoustic phenomenon which expresses the alternation of the sounds is in no case so conspicuous as to become evident on auscultation. Generally it is within the limits of perceptibility and if it is not deliberately sought it will be overlooked."[4] Six of these 7 cases were detected by auscultation before any graphic record was obtained. It appears that failure to recognize alternation by auscultation over the precordium when it can be detected lies in a large part in the same reasons for its lack of recognition by use of the blood pressure cuff: it is not deliberately sought. Objective records of heart sounds showing the frequency of sound alternation must modify the view that such changes are exceptional. It is a frequent occurrence often occurring only to a mild degree easily overlooked by auscultation.

The differences to be noted when searching for alternation are in intensity and pitch. The one sound is more intense, higher in pitch, and "dryer" than the same sound in the following cycle.[4] These same authors state that a slight irregularity independent of the regular cardiac rhythm, is perceived by the ear. It is supposedly due to a real anticipation of the second sound in the cardiac cycle in which a weak first sound is produced by the shorter duration of the systole of this beat.

Differential Diagnosis. Little need be said here concerning differential diagnosis. The differentiation of pulsus bigeminus due to regularly recurring premature beats with resultant changes in the blood pressure are well known and easily ruled out by precordial auscultation for signs of premature beats and by electrocardiography. While the distance between the large and small beats is less than the distance between the small and large ones in pulsus bigeminus due to premature beats (the small ectopic beat is premature and closer to the preceding normal or large beat), any change which may be present in pulsus alternans is

the reverse due to the delayed opening of the semilunar valves and the slower pulse wave velocity of the small beat. This was first noted by Traube and, as Lewis[22c] states, it may be conspicuous, slight or absent. The misdiagnosis of pulsus alternans for premature beats and its occurrence in several beats following a premature beat should not be confused.

Other confusing factors are uncommon. The changes produced in systolic blood pressure levels by respiration, particularly when the respiratory rate is about one-half the heart rate, are easily recognized and ruled out by controlling respiration. Possible confusion with a dicrotic pulse is easily differentiated in that the pulse would be timed at twice the cardiac rate as determined at the heart. Again, when the alternation is so severe that no ejection from the left ventricle occurs with the weak contraction, alternation will not be recognized in the pulse, but a rate exactly one-half of the heart rate will be found. This latter condition must be very rare. Excellent examples may be found in the experimental curves of Lewis.[22c]

Alternation of the auricle has been described and recognized by alternate changes in the *a* wave of the jugular pulse. While such changes in the *a* wave may be indicative of auricular alternation, either concordantly or discordantly with the pulse, it may be due to the auricular and ventricular systoles coinciding, alternate auricular beats falling with the stronger or weaker beats of the ventricle. Under these circumstances, it cannot be taken as a measure of the force of the auricular contraction.[22c]

Clinical Significance. Pulsus alternans is of great clinical importance diagnostically and prognostically. White[41b] describes it as practically the only pathognomonic sign known of weakness or failure of the left ventricle. With the now recognized necessity of detecting left sided heart failure before peripheral edema and the other signs of right sided heart failure make their appearance, the increasing importance of pulsus alternans as a diagnostic aid will be appreciated. Its presence would be helpful in differentiating from left ventricular disease disorders of the lungs which produce dyspnea, as well as in following the course of such conditions as hypertension, which are known to put a strain upon the left ventricle.

From the prognostic viewpoint, patients with pulsus alternans should be divided into two groups. The first group includes those patients with alternating pulse and extremely rapid hearts, particularly paroxysmal tachycardia. Little is known of the mechanisms and associations of alternation in such instances and its prognostic value in such patients is not definitely known. When the tachycardia stops, the alternation disappears and the patient's outcome is apparently conditioned by factors other than the pulsus alternans. Whatever its significance in such patients it is not a grave prognostic sign and probably indicates an extreme burden even upon a normal heart.[22b]

The second group consists of those patients in whom pulsus alternans accompanies a slow heart rate. In these patients the alternation generally occurs when the rate is over 90 per minute and may disappear as the rate falls to approximately 70 per minute.[21] Here the prognosis for life is about 1 to 2 years, but exceptional instances of 5 or more years are recorded.[21,37,44] The report of Thompson and Levine[37] typifies

the consensus in the literature. In 117 patients with the constant variety seen over a 12-year period, there were 71 with known dates of death. Of the 71 patients only 5 were under 40 years, and in them the average duration of life after detection of alternation was only 6 months. Those of 70 years or older lived on an average of 19 months, and further analysis disclosed that the older the patient was at the time of detection of the alternation the longer the life after detection. Analysis according to sex showed that 50 males averaged 17 months after detection; 21 females only $8\frac{1}{2}$ months.

Other interesting findings occurred in this same series. The average length of life after detection in patients with hypertension was $15\frac{1}{2}$ months, in patients without hypertension, 9 months. This conforms with Hewlett's experience.[14] However, at very high pressures, this relationship did not hold. In general, then, in this group prognosis was better with hypertension, either systolic or diastolic, until very high pressures were reached. Prognosis was also more serious with frank signs of congestive heart failure, but this state in itself adds much weight to the prognosis. Likewise those with coronary occlusion averaged only $5\frac{1}{2}$ months, those with coronary artery disease and no occlusion $17\frac{1}{2}$ months. The presence of intraventricular block in the electrocardiogram did not seem to increase the gravity of the picture.

Electrical Alternans. The term, *electrical alternation*, has come to mean[6] a regular alternation at equal intervals in amplitude or contour, or both, of the varying phases in the electrocardiogram. It can be seen that such an inclusive statement brings under the term, *electrical alternans*, a great number of electrocardiographic changes, including alternation of the *P* waves alone, which is rare, of *A–V* (*PR*) and intraventricular conduction[2,11,27] of *R*, *S*, and *T* wave amplitude. *T* wave alternation, alone or with similar changes in the *QRS* group (particularly *R* amplitude), appears to be most frequent. *S* wave alternation is more rare.[24] Like the mechanical variety, it is usually transient and varies in degree and constancy, but it is less frequent. At the University of Illinois cardiac clinic[6] the condition did not occur once in 6000 records. Another group[11] found it only once in 10,000 tracings. Likewise, the paucity of reports in the American literature tends to confirm the rarity of its occurrence, although the number of cases in the Continental literature[3a,40] indicates that it is probably more frequent than American observers suspect.

In electrical alternation, problems in differential diagnosis similar to those in mechanical alternation must be considered. For example, bigeminy of ectopic beats and the effects of respiration may produce voltage alternations but these are easily differentiated by those familiar with the electrocardiogram. Such conditions as bidirectional complexes[23,32,35] and alternating bundle branch block[18,20] are not generally considered in the term, *electrical alternans*, although their inclusion in each case would be merely a matter of definition, and pulsus alternans has been described in alternating bundle branch block.[7] In both, and especially the former, the prognosis has been very grave.

Although mechanical alternation is seldom accompanied by electrical alternation, the electrical variety is seldom unaccompanied by the mechanical. The pulse may alternate discordantly or concordantly with the electrocardiogram. Isolated electrical alternation, that is electrical

without accompanying mechanical alternation, has been known for years. Mines[26] first described it in the frog in 1913, and subsequent clinical reports had all been European until 1936 when the first American report[11] appeared. Since that time several additional American ican reports[1,6,27] have been made. In one case[11] there was no alternation detected in the pulse, apex beat, or heart sounds, and the alternation was precipitated by changes in respiration. In this patient, *QRS* and *T* alternated discordantly. Autopsy showed multiple microscopic myocardial infarcts. In another, in whom *QRS* changes only were noted, small carcinomatous metastases were found in the heart. The authors concluded that malnutrition of the myocardium was responsible for the electrical disturbance and that these changes had the same significance as mechanical alternation. Alternating foci of impulse initiation and alternating paths of conduction of impulses from one focus can account for alternation in the form and height of complexes in the electrocardiogram, as Brody and Rossman[1] point out. In the past, electrical alternation like the mechanical variety has been described in experimental and clinical coronary disturbances and there has been adequate confirmation of these points by European workers. The close association of the etiologic factors causing both types of alternation, as well as the frequency of their occurrence together, indicate that they are many times probably of the same significance. Still their appearance independently from each other leaves the possibility of their having different clinical significance, particularly in forms other than those involving the amplitude of *R* and *T* waves. As yet there are not sufficient data for the adequate handling of these problems statistically. Poumailloux[33b] feels that there are two forms of electrical alternation having different significance. Alternation of the *T* waves, with which *QRS* alternation may be associated, has the same significance as mechanical alternation, and alternation of the *QRS* complex or any of its components, which is transient, is totally unrelated to mechanical alternation. There is considerable controversy on these points.[3b,19a]

Should electrical and mechanical alternation be expressions of the same physiologic disturbance, may we account for the occurrence of one in the absence of the other? May the same phenomenon in various instances be demonstrated best by electrocardiography and in others by mechanical means? Mines[26] has offered an explanation. He calls the whole musculature under consideration V and the muscle whose excitability is lower than the rest v. The latter portion must be subdivided accordingly as it chances to respond to the odd or even series of excitations. The alternating series will usually run V–v_1, V–v_2, V–v_1, V–v_2, etc., and not simply V, V–v, V, V–v. If $v_1 = v_2$ so that mechanical effects are alike, yet owing to their different positions in relationship to the electrodes, their effects on the electrocardiograms may be dissimilar. Similarly, the mechanical events may be favorable for alternation when the electrical derivations fail to show changes. Likewise, one may see that the disappearance of electrical or mechanical alternation would not necessarily be a sign of improvement, for those segments of muscle failing to respond at every other beat may so increase, rearrange, or become progressively impaired that equal effects result in each beat. Alternation would then disappear even in the face of a progressively downward course.

Feldman[6] has added another consideration to the problem of electrical alternation. He reported electrical alternation involving the *QRS* complex and at times the *PR* interval in a patient with pericardial effusion due to carcinomatous metastases. Mechanical alternation was not detected in blood pressure determinations. Autopsy revealed no coronary disease, no extensive myocardial fibrosis and no metastases to the heart, leaving the effusion as the probable cause of the alternation.

That pericardial effusion may lower the voltage of the electrocardiogram is well known, both in experimental[17] and clinical[12,31] cases. If the hydrostatic pressure is elevated adequately in the perciardium, and this appears to occur clinically, it may lead, as shown experimentally, to interference with coronary circulation (cardiac tamponade) in the face of normal coronary arteries.[17,34] The hydrostatic pressure developed varies widely and depends upon such factors as rapidity of filling, actual amount of fluid, and distensibility of the sac. Hence, as Feldman states, it is easily conceivable that the anoxemia thus produced may, under certain circumstances, interfere with the intrinsic circulation of certain regions of the heart muscle and thus lead to alternation. If this is true, it may be that under such conditions the alternation would have the same prognosis as the pericardial effusion, whatever its cause and extent.

One must speak with caution concerning the prognostic importance of the various types of electrical alternation. Those occurring in paroxysmal tachycardia, as in the mechanical type in this condition, have apparently a like prognosis. With slower heart rates, however, one must, in the face of its known association with serious myocardial disease, view it as an ill omen.

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PEDIATRICS

UNDER THE CHARGE OF

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PNEUMONIA IN CHILDHOOD.

Pneumonia in children is generally regarded as a less serious condition than pneumonia in adults. This viewpoint may be only relatively accurate. Very virulent strains of infection may occur in children and the threat against life may be equally as grave as a similar infection in adults. However, for the most part the heart, the kidneys and other organs of children are better able to withstand the toxic effects of the disease because they have not been subjected to the stresses and strains of repeated infections, overwork, overworry or dissipation that constitute the life of an adult.

In children, certain conditions may predispose to a high mortality rate. Gruninger and Droste[10] point out that the death rate from pneumonia is comparatively high in children during the first year of life. In their clinic, a noticeable decrease in the mortality rate had been observed during recent years. In order to determine what factors were responsible for this decrease, they analyzed the cases of pneumonia that were cared for during the years of 1924, 1926, 1928, 1930, 1936 and during the first half of 1937. The cases totaled 1645. The mortality varied with the various types of pneumonia. In lobar pneumonia, they found that the uncomplicated involvement of one lobe healed with or without treatment. Such a type of pneumonia is not suitable for the evaluation of a therapeutic procedure. Excluding lobar pneumonias and abscess-forming pneumonias, they found that in all other types the infants with rickets had a higher death rate. They observed that the fresh air treatment produced a noticeable decrease in the mortality of different types of pneumonia. In the whooping-cough pneumonias and in the complicated bronchopneumonias the favorable

effects of the fresh air treatment could be increased by the viosterol treatment of the children having rickets. The successful viosterol treatment of pneumonia in rachitic children was further corroborated by their favorable experiences with the massive dose of vitamin D_2 in rachitic children with pneumonia.

During a $5\frac{1}{2}$ year period 459 cases of pneumonia were studied by Ellenberg and Martin.[7] Of these cases 89 were 1 year or under, and 48 between 1 and 2 years of age. Further statistical study showed that 40% were under 3 years of age, while 50% were under 4 years. The smallest number of cases were recorded in the ninth, tenth, eleventh and twelfth years of life, while the peak was reached in the first year. Lobar pneumonia was more prevalent among the male children as shown by 260 males being affected as compared with 199 females. While the comparative figures in the literature are scarce they conform to this ratio. As regards seasonal incidence, the greatest number of cases were recorded during the late winter months and the greatest morbidity for the entire period of study was found to be in March with April coming a close second, while the smallest number of cases occurred in July. During the $5\frac{1}{2}$ years covered by this study the peak of morbidity occurred each year in a different month. In this series of 459 cases of lobar pneumonia 40 died, a mortality rate of 8.6%. Of these, 18 died during the first 48 hours after admission and were regarded as non-institutional deaths and this brought the mortality rate down to 4.7%. They found that the mortality rate was higher in children under 2 years. These gave a death rate of 24% as compared with 21.1% in the children over 2 years.

Nedzel[14] claimed that the presence of pneumococci in the upper respiratory tract is not a sufficient cause for the development of lobar pneumonia, but that a dysfunction of the upper respiratory tract must precede the development of the pneumonia and this disturbance must be of such extent or type as to involve the whole respiratory tract and lead to the lowered resistance of certain tissues. This occurs when normal circulation of the blood is impaired. The vascular contraction of mucous membranes of the respiratory tract, which accompanies that of the skin during exposure, causes a delay in the mobilization of the defensive forces, and as a result of this disturbance in the irrigation of the tissues they become impaired and the bacteria present find a favorable field for their development. The exposure of the body to cold is a powerful factor that not only causes the contraction of blood vessels of the skin, but also, on account of the existing splanchno-peripheral balance, involves the blood vessels of the mucous membranes of the whole tract and causes stasis and edema in the lungs. Such a condition favors the multiplication of pneumococci.

Pelfort[17] in discussing the frequency and localization of pneumonia in the infants under 1 year, maintained that lobar or croupous pneumonia is of frequent occurrence in the first year of life. He observed 64 cases from 1923 to 1935 among 300 children under 3 years of age with pneumonia. In this period, he followed practically every case with Roentgen studies. In this way he found 38 different localizations of the lobar distribution in 30 cases. The upper lobe of the right lung was the most frequent site of involvement. The lower and upper

lobes of the left lung came next in frequency and finally the middle and lower lobes of the right lung.

Joppich[12a] showed in his study the variability of pneumococcic manifestations in infancy. Many times the Roentgen rays did not give an accurate picture of what was occurring. He tried to show why some types of pneumonia are lobular and some globular. Some think that the difference is due to different types of pneumococci while others think that it depends on the reaction of the human organism. Among the autopsy material several instances were encountered in which both types of pneumonia were present. This led him to believe that the question could not be answered.

According to Robertson[18] very little is known concerning the optimum conditions for the inception of lobar pneumonia in the human being. That some disturbance in pulmonary function precedes the onset of this disease in the majority of cases seems probable in view of the frequency of antecedent acute infection of the upper respiratory tract, but the manner in which such infection lowers the resistance of the lung to invasion by pneumococci can only be conjectured. Directly opposed to any influence of previous infection is the fact that in a considerable number of cases lobar pneumonia develops during a period of apparent good health. He was able to produce in dogs a lobar pneumonia closely resembling that which occurs in humans. This was done by implanting pneumococci suspended in a starch-broth paste into the terminal air sacs of the animals. The pneumococci were dispersed from the site of implantation principally by the edema fluid of the early lesions which spread peripherally through the contiguous air passages and the pores of Cohn. The experimental lesions developed in practically the same manner as the disease develops in the human. He observed a striking histologic change both in man and in the dog at the time of recovery. This consisted of the transformation of certain of the fixed tissue cells into free macrophages which engulf and destroy the pneumococci much more effectively than do the neutrophils. The macrophages are dependent on opsonins for their antipneumococcic activity. The mechanism of recovery seemed to be of dual nature, consisting of a generalized process which acts to localize the infection and control or prevent bacteremia, and a local process which is the macrophage reaction whereby the lung is enabled to rid itself of the invading microörganisms. If both processes are effective, recovery results. If either one fails, death ensues. In experimental pneumonia, one attack conferred immunity to subsequent infection. This immunity lasted for months. The basis of such an immunity seemed to rest on the greatly accelerated macrophage reaction. After recovery a high degree of local immunity can be demonstrated in the involved lobes. It persists as long as the macrophages are present in the alveoli.

Andrews[1] made comparison of numerical with causative frequencies of types of pneumococcus which had been recovered from children with lobar pneumonia and separated them into 3 etiologic groups, the distribution of which, among patients with and without pneumonia and among other members of the same families, indicated a corresponding diversity in their etiologic significance. The A types appeared causative in all patients with lobar pneumonia from whom they were recovered.

They were associated with a relatively high incidence of pneumonia in infected persons, high mortality among infants, marked evidence of familial dissemination when the concurrent pneumonia was ascribed to these types and relatively low incidence in families without pneumonia or in those in which the patients did not show the same types of pneumococcus. Intermediate or B types appeared causative in many, but not all, of the children with lobar pneumonia from whom they were recovered. In comparison with the former group they showed a lower incidence of this disease in infected persons, lower mortality among infants, less evidence of familial dissemination when the concurrent pneumonia was ascribed to these types and a relatively high incidence in families without pneumonia or in those in which the patients had pneumonia ascribed to heterologous types. The least active types were listed as C types and appeared to be responsible for lobar pneumonia in few of the children from whom they were recovered. Evidence of their familial dissemination was uncommon, but these were the types most often recovered from persons coming in contact with patients whose pneumonia was ascribed to heterologous types.

Nemir, Andrews and Vinograd[16] studied clinically and bacteriologically 1033 patients with pneumonia during four pneumonia seasons. In addition, they studied 425 patients having pneumococci in the respiratory passages but who did not have clinical pneumonia. They found most frequently pneumococci of Types I, VI, and XIV. These 3 types comprised 41.6% of this series. They noted the age distribution of certain pneumococci. Type I was found rarely in patients under 2 years. On the other hand, Type XIX was cultured almost entirely from patients under this age. Types VI and XIV were more prevalent in infants and in the preschool group. Types XIX and VI occurred most frequently (30%) in the patients who did not have pneumonia. Types I and XIV were rarely obtained from this group. Pneumococci of types III, VI and XIX were found almost as commonly in patients without pneumonia as in those with it. The pneumococci cultured from patients with bronchopneumonia were of the types commonly found in healthy carriers and in patients without pneumonia. The Type XIV pneumococcus was an exception, being present in 9.6% of the patients with bronchopneumonia. Two-thirds of these patients had streptococci alone or in combination with the types of pneumococci found in common carriers.

Joppich[12b] claimed that the Types I and II pneumococci must be regarded as the chief exciters of lobar pneumonia in the adult while all of the other types which he collectively groups as Type X cause focal pneumonia. In the infant and small child the dependency of the form of the pneumonia exciter is not so strict. It has been proved that certain infantile pneumonias with a cyclic course broken by a crisis and also real lobar pneumonia including forms with empyema in larger children are caused by Type X. This fact has been tentatively explained by a hypersensitivity of the infantile organism to the pneumococcus in general. In the light of this hypothesis, focal pneumonia would come under the normergic form and lobar pneumonia would come under the hyperergic form. In this way many of the features of the latter would seem to find an easier explanation. Bullowa and

Greenbaum[5] studied the age distribution and the mortality for the 32 types of the Cooper classification in 539 cases of pneumococcic pneumonias during a period from 1928 to 1934. During this time 1000 cases of pneumonia were observed in children brought to the Harlem Hospital. They said that some types of pneumococci which attack children are more important than others, and some types select children of certain ages for attack. The important types are I, VI, XIV, and XIX. They grouped their studies of type incidence to age by using the following age groups; from birth to 2 years, from birth to 6 years, from 2 years to puberty and from 6 years to puberty. They found the Type XIV the most frequently encountered type of pneumococcus. It was isolated in 83 (about 15.4%) of 539 cases. Type I was the next most frequent as it was seen in 79 cases or almost 15%. Type VI was observed in 10.2% of the group. Types IV, V, III, XIX and VII were seen in more than 3% of the cases in this order of incidence. In 70 cases, the "X" or unclassified type was observed and there were 15 cases of multiple infection or invasion by pneumococci and other organisms or by pneumococci of two types. When the patients were divided into those under 2 years of age and those over 2 years it was found that 262 (almost one-half) were infants under 2 and that 277 were between 2 and 12 years. The types of pneumococci causing pneumonia of infants under 2 years were distributed as follows: Type XIV caused 47 (17.9% of the cases); Type VI caused 34 (13%); Type XIX, 19 (7.3%) and Type I only 13 (5%). In 39 cases the organism was unclassified and there were 7 instances of multiple invasion. In the 277 cases in which the patient was over 2 years of age the dominant type was I. It was seen in 66 cases or almost 24%, which approaches the frequency of this type in adults. Type XIV was isolated in 36 cases (13%); Type V in 22 cases; Type VI in 21; Type IV in 17; Type III in 16 and Type VII in 12 cases. Types II, VIII and XIX were each observed in 6 cases and there were 8 cases of multiple invasion. The most important type of pneumococcus obtained from the infants under 2 years of age was Type XIV. After the age of 6 years it gave way in dominance to Type I. Type VI, which was important before the age of 6 years, was persistently so beyond that age period. Type XIX, which occurred frequently before the age of 2 years, was not seen after the age of 6. Type XVIII was noted chiefly before the age of 6. Types III, IV, V, and VII were seen equally distributed in children of all age groups. These observers found that some types of pneumococci caused fatal involvement more frequently than others. Some of the types designated by the higher numbers are infrequently isolated but cause a fatal outcome more often than do types which are commonly met. They found a very high death rate in the rare Types XVI, XVII and XXIII.

Fleming[9] made leukocyte counts during the course of the disease in 147 cases of lobar pneumonia. He found the distribution according to types of pneumococcus as follows: 58 cases of Type I with 4 deaths; 51 cases of Type II with 10 deaths; 7 cases of Type III with 5 deaths and 31 cases of Group X with 2 deaths. He found that during the first 3 days of illness leukocytosis with a white cell count greater than 20,000 was characteristic of pneumonia due to Type I, while the

count in pneumonia due to Type II was usually below 20,000. The count in most cases of pneumonia due to Group X strains resembled those with Type I as the causative factor, while that in pneumonia due to Type III resembled the count in severe pneumonia due to Type II in which it was low. He found that the average daily counts in the various types of pneumonia showed separate levels during the early days of the illness. This makes it possible to make a differentiation of pneumonia due to Type II from that due to Type I and from that due to Group X strains. He used for prognostic purposes the leukocyte count in conjunction with the type of organism, the age of the patient and the duration of the illness.

In a discussion of the course of lobar pneumonia in children Ewstatiew[8] said that the onset of pronounced lobar pneumonia in the child, contrary to that in adults, is often preceded by fatigue, nosebleed, headaches, vomiting, cough and other symptoms which cannot in good faith be considered as prodromal symptoms of pneumonia. As to the defervescence, it is seldom definitely critical. Often it is pseudocritical or preceded by one or several sharp drops in temperature before finally dropping to normal. In some cases, the subsidence of the temperature is definitely by lysis. He pointed out that pneumonia is a septic disease and stated that fever probably exists as long as there are exciters in the blood. The pneumonic focus is the expression of localization of the disease and as such is comparable to a pulmonary exanthema in the sense of Pirquet. The course of the disease in the child expresses this in a manner which indicates that the defense mechanism, especially the reticulo-endothelial system, is in an undeveloped condition. It has not had time nor opportunity to collect specific and non-specific immuno-biologic experience. In some children, the diagnosis may be difficult for some days. Savoye[19] commented that there are cases of pneumonia in children in which the pathologic process shows no signs for several days after the onset of the disease but later gives typical signs. There are other cases in which the patients go through the entire course from onset to complete recovery without any demonstrable physical findings. From the roentgenologic point of view the pneumonia in these patients is not all central. Typical triangular shadows with bases at the peripheries of the lungs have been observed in which no signs were present. It is believed that physical signs are produced as the result of congestion about solid, hepatized areas. When the latter are present without the former, air cannot pass in and out of alveoli to produce blowing breathing and crepitations.

As a diagnostic and prognostic aid Brooks[4] used a new method which he devised. He found that early in pneumonia there is a greatly accelerated blood sedimentation rate, which gradually returns to normal as the patient recovers. The normal curve does not occur until all signs obtained by roentgenologic and physical examination are normal. This indicates that the sedimentation rate is highly sensitive to a pathologic condition in the lungs. In cases of severe pneumonia in which the clinical condition progresses unfavorably the sedimentation is more abrupt and falls to still lower levels. This type of curve constitutes a bad prognostic omen.

Langley, Mackay and Stent[13] examined the blood serum of patients

suffering from pneumonia for agglutinins. They also tested the effect of serum therapy on the occurrence of agglutinins. They found that agglutinins are recognizable in the serum of the patient with lobar pneumonia when the infection is due to organisms of Type I or II. These agglutinins are closely related to recovery as they are absent in cases in which the infection is fatal. After intravenous injection of 20,000 units each of concentrated Type I and Type II pneumococcus serum, agglutinins for the heterologous organisms are readily recognized in the patient's serum but may disappear with the injection of homologous serum. These authors suggested that the test for agglutinins is a reasonable means of determining the number of doses of serum required in any patient.

In the current literature are found other methods of treating pneumonia. One such method is discussed by Bolton[3] who reported a series of patients, a number of whom he treated by administering stock vaccine. There were 168 patients with primary pneumonia and of these 91 were admitted within the first 3 days of the disease, and of these, the vaccine was given to 32. Vaccine treatment reduced the duration of the uncomplicated pneumonia by an average of 3 days. He found that recovery within 5 days of the development of the pneumonia was much more likely if the vaccine had been administered. Certain of the cases responded immediately to vaccine with a crisis and with marked improvement in the clinical condition in 12 hours. There seemed to be some risk in administering large doses of vaccine to patients who gave a history of chronic cough prior to the onset of the acute condition. In his series, the mortality was 13 of the 59 control patients who did not get vaccine treatment while only 6 of the 32 who received vaccine died.

Both statistical evidence and clinical observations of individuals in a large series of patients has convinced Nemir[15] that Types I and XIV sera are valuable and effective aids in the treatment of pneumonia in children. In a smaller series, Types VII, V and II have been shown also to be valuable. Even though dramatic response to serum therapy may be obtained, other considerations are important before making the decision to use antipneumococcus serum in children. Since the mortality rate of lobar pneumonia is low in children more than 2 or 3 years of age, a specific therapeutic agent is not imperative. Treatment of patients with serum late in the disease is useless in patients less than 12 years as it has little effect on mortality and none on complications. A bacteremia, although discovered late, is usually helped by the use of serum and should be treated in this manner. This is a rare complication in children but when it is present it indicates very severe and overwhelming infection. The author recommended the use of homologous serum early in the disease in infants severely ill with Type XIV pneumococcus pneumonia. This is especially important because in the age group below 2 years the mortality rate is high. Indiscriminate use of serum for moderately or mildly ill patients is not advisable because of the sensitization to horse serum. With the production of satisfactory sera from rabbits this objection may be removed.

Harper[11] instituted artificial pneumothorax without fatality in the treatment of 22 children with lobar pneumonia. Their ages ranged from 15 months to 15 years. Most children required sedatives, and

for this purpose morphine gave excellent results. A rise in the interpleural pressure averaging +4 cm. of water was observed when patients who had been lying on their sides during the injection of air were turned to lie on their backs. Since the extent of the rise varied with the age and other factors, it seemed best to treat the children in the supine position. It must therefore be remembered in comparing these data with those of other authors that the readings of interpleural pressure are from 0 to +7 cm. of water higher than they would be if the patients had been lying on their sides, with the collapsed lungs upwards. In general, the results of compression on the pneumonic lung were encouraging when early and good collapse was obtained and were of doubtful value when compression was either delayed or incomplete. More complete and more rapid compression of the lung without discomfort to the patient was obtained by decreasing the rate of injection of air used in the early cases to a speed of from 7 to 9 cc. of air per minute, but at the same time increasing the amount of air especially on the initiation of pneumothorax. These observations suggested that the interpleural pressure required to give early and good collapse varied both with the age of the child and the extent of the pneumonic infiltration. Tentative levels of pressure were suggested which gave satisfactory results in children older than 6 years. The interpleural pressure was pushed slowly towards these tentative levels, with reliance on the symptomatology, especially beginning dyspnea and on evidence of mediastinal shift for warning to stop. In all cases in this series respiratory distress passed away within a few hours. At the first renewal of air, given after an interval of about 4 hours, the pressure was carried to higher levels without causing disturbing symptoms. The author stated that this work did not establish the value of artificial pneumothorax therapy in lobar pneumonia in children. A technique has been developed for the therapeutic use of this procedure, which when satisfactorily carried out, gave encouraging results. In evaluating the results it would be well to keep in mind that the technique developed as the work progressed and that future patients should benefit from the technical improvements.

Another contribution to the therapy of pneumonia was the use of blood transfusions. Arena[2] stated there is little ground for the belief that the circulation will be embarrassed by transfusion at a time when the total circulating volume of blood is decreased. In the past 3 years he made efforts to give one or more transfusions to all infants and children on his service that had severe primary pneumonia, whether or not they had anemia. Because of the difficulty of securing donors 35 of these patients did not receive blood and consequently served as controls. The other 24 had one or more transfusions of citrated blood by the gravity method with a maximal amount of 20 cc. per kilo of body weight. The clinical symptoms, hemoglobin content and red and white cell counts for the two groups were almost identical. The only difference was that in the group who received transfusions there were probably more ill patients and more infants so that the expectations in this group were worse. However, prompt and marked improvement usually followed the transfusion, and the patient appeared more comfortable. The temperature fell by crisis in 24 hours of the transfusion

in 15 patients and in 48 hours in the other 9. The average interval between the onset of the disease and the crisis or lysis for this group was $7\frac{9}{10}$ days. Four of these children had the complication of suppurative otitis media and 1 died. For the 35 patients who did not receive transfusions the average interval between onset and the crisis or lysis was $9\frac{9}{10}$ days. Of these children, 3 had the complication of empyema, 9 had otitis media and 5 died. The severe dyspnea and cyanosis, which many of these children had, were improved instead of made worse by the transfusion. No circulatory embarrassment was noted during or after the procedure. After the transfusion several of the patients had an immediate rise in temperature, which was usually followed by an immediate crisis. The explanation of the beneficial effect of the blood transfusion is not known. It seems doubtful that the correction of anemia could be a factor. The results were as good in the patients with severe anemia as in those with moderate anemia. Apparently the only contraindication for transfusion in children is damage to the kidneys.

Degwitz[6] discussed the mortality rate in 2 groups of children who had bronchopneumonia. The first group comprised 334 which were treated during the time the fresh air treatment was not yet used. In the second group of 424 children, the fresh air treatment was used. The ages of the children, the percentage of severe cases and the incidence of complications were about the same in the two groups. Certain indispensable nursing and medicinal measures were about the same for the two groups. The first group was treated in ordinary wards while the second group received fresh air treatment in open-air verandas or in open-air rooms. A comparison of the mortality rates in the two groups proved that in the open-air group there were only one-third of the deaths that occurred in the other group. It would seem, therefore, that there was a distinct advantage in this method of treatment.

The use of sulphanilamide in the treatment of pneumonia has been discussed at some length in the literature. Its value in children is as great as its value in adults especially in cases in which specific type serum cannot be employed. The limitations of space do not permit discussion of this valuable treatment which deserves consideration by itself.

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PHYSIOLOGY

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The Occurrence of Chemotaxis in the Slime Mold. DALE REX COMAN (Laboratory of Pathology, University of Pennsylvania). Investigations of chemotaxis in polymorphonuclear leukocytes have left unanswered certain fundamental questions. To understand chemotaxis we should know something about the nature of substances which cause it, the organisms or cells which show it, and the mechanism concerned.

In the hope of obtaining such information, we sought an organism of a relatively low order of life, in contrast to highly specialized cells, and one which could be adapted to both gross and microscopic study. The slime mold, *Physarum polycephalum*, was chosen and a culture of this organism was obtained from Professor Seifriz of the Botany Department. The mold grows over a moist surface in soft yellow strands and masses. Microscopically, it appears as a syncytium of granular protoplasm which shows rhythmic streaming.

In gross experiments, the mold, growing on agar plates, was repelled by hydrogen and hydroxyl ions, was attracted by dextrose, and was indifferent to sucrose and sodium chloride. It was also indifferent to crystalline egg albumen and insulin. Fifteen to 20 plates were used for each substance tested, and the same result was obtained in all the plates.

In microscopic experiments, a piece of the mold was attracted by one substance and then caused to reverse its direction of locomotion by introducing a repelling substance. Evidence obtained from such experiments throws doubt on the surface tension theory of chemotaxis and suggests the probability that the organism reacts to a stimulus transmitted throughout its substance.

Persistent Diabetes Following Injections of Anterior Pituitary Extract. F. C. DOHAN, and F. D. W. LUKENS (George S. Cox Medical Research Institute, University of Pennsylvania). F. G. Young (Lancet, **2**, 372, 1937), has recently reported the production in dogs of diabetes which continued for months after the cessation of daily intraperitoneal injections of increasingly larger doses of anterior pituitary extract. Using the technique described by Young, we have produced an apparently permanent diabetes in 3 of 8 dogs after the several weeks during which injections were given. During this period, there was a marked hypoglycemia and glycosuria. The severity of the postinjection diabetes varied with the individual dogs. Two dogs excreted glucose approximately equal in amount to the available carbohydrate in their food. During fasting or fat feeding there was very slight glycosuria or ketonuria—much less than that of the depancreatized dog. The responses to diets, glucose tolerance tests and insulin tests were reported. Island lesions were noted in one animal suitable for this observation (in press, Am. J. Physiol.).

The Action of Insulin Upon Protein and Carbohydrate Metabolism of Surviving Liver Slices of Normal and Diabetic Animals. W. C. STADIE, F. D. W. LUKENS, and J. A. ZAPP (Laboratory of Research Medicine and the Cox Institute, University of Pennsylvania). Experiments were made on surviving liver slices equilibrated in phosphate buffer for 2 hours at 38° C. Oxygen consumption, the respiratory quotient, the total fermentable carbohydrate, and the urea formation were measured. Various amino acids were used as nutrients and the effect of insulin in the medium upon the above noted metabolites was measured. The tissues used were from normal rats, normal cats, diabetic cats, hypophysectomized cats, "Houssay" cats, and cats made diabetic by the injection of anterior pituitary extracts.

The following summarizes the findings: (1) In the normal rat or cat we have been unable to find significant inhibition of urea formation by insulin when the medium contains no added nutrient. In the same circumstances, we have been unable to demonstrate any inhibition of urea formation in the diabetic cat liver. (2) With *dl*-alanine in the medium we have found with considerable regularity in the normal rat and cat that insulin produces an inhibition of 10 to 15% of the extra urea formation which *dl*-alanine produces. In the diabetic cat, we have found essentially the same thing. However, the insulin effect is not greater than that found in normals. (3) Insulin has no inhibitory action on the urea formation owing to the presence of the naturally occurring amino acids. With the non-natural amino acids there is found quite regularly an inhibition of urea formation by insulin. (4) Injection of anterior pituitary extracts sometimes causes marked increase of the deaminating power of the liver. Insulin inhibits markedly this enhanced urea formation, but the effects are inconstant. (5) No effects of insulin upon carbohydrate synthesis by the liver have been observed in normal rats, cats, or diabetic cats.

Transient Ventricular Fibrillation in Man. WILLIAM G. LEAMAN (Department of Cardiology, Woman's Medical College of Pennsylvania). Transient ventricular fibrillation is demonstrated in an electrocardiogram from a patient, aged 76, suffering from hypertensive cardiovascular disease and presenting varying grades of *A–V* block. During a typical Adams-Stokes seizure the tracing showed, in addition to other arrhythmias, a period of ventricular fibrillation lasting 42 seconds. Recovery occurred through the development of an idioventricular rhythm with ultimate reëstablishment of a 2 to 1 heart block (auricular rate 80, ventricular rate 40). The patient left the hospital in fairly good condition. However, ventricular fibrillation, as viewed by the physiologist in the larger, intact laboratory animal, is nearly always an irreversible state produced by the manipulation of the heart, electrical stimuli, occlusion of the coronary arteries, heating, alteration in vagal or sympathetic tone, and the toxic action of certain drugs. For this reason, cases demonstrating the mechanism with recovery in man should always be carefully studied. The number reported in literature is small (18 instances). Nearly all patients had advanced heart disease with associated complete *A–V* block and Adams-Stokes syndrome. There is still considerable controversy in regard to the electrocardiographic diagnosis

of ventricular fibrillation in man. We believe it can be diagnosed when the waves present the extremely bizarre appearance seen in the motion picture film of this tracing with total irregularity of rate and rhythm of the type obtained when the lack of coördinated contraction of ventricular fibrillation is actually observed in the exposed dog heart. We conclude from a study of the record of this case, and of a similar one from our own laboratory, in a man of 66 suffering from the same type of heart disease that, in man, ventricular fibrillation can be a reversible process with complete recovery possible, and that such occurrences are more frequent than the scant number of reports in the literature tend to indicate.

CORRECTION.—In Dr. Schiødt's article on "Observations on Blood Regeneration in Man," the footnote on p. 639 of the November, 1938, number should read: "In 17 patients" instead of "77 patients."

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